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# THE BLOOD CHEMISTRY DURING PREGNANCY

By H. J. Stander, M. D.

*(From the Department of Obstetrics, Johns Hopkins University and Hospital)*

From a survey of the literature it appears that routine chemical analysis of the blood has been comparatively little utilized in Obstetrical Clinics, with the result that the importance of blood chemistry in normal pregnancy and particularly in women suffering from certain complications of pregnancy has only recently become apparent.

In 1917 Folin reported analyses on the blood of about 100 pregnant women, and found that the non-protein nitrogen is seldomly over 30 mgms. per 100 c.c. of blood, the urea nitrogen representing from 20 to 35 per cent of the non-protein nitrogen.

A few years later Caldwell and Lyle published their results on a series of 150 analyses on pregnant women. Their figures for urea are decidedly higher than those of Folin, their average being 24.6 mgms. per 100 c.c. of blood, while Folin's figures varied from 10.7 to 19.2 mgms.

De Wesselow, in 1922, examined about 50 normal pregnant women and found values similar to those reported by Folin.

E. C. Williams has just shown that there is a decided drop in the urea content of the blood during the middle three months of pregnancy. Her average figures during the whole term of pregnancy (from 100 analyses) are:

Non-protein nitrogen, 25.2 mgms. per 100 c.c. blood
Urea, 19.5 mgms. per 100 c.c. of blood

Ratio, $\frac{\text{urea nitrogen}}{\text{non-protein nitrogen}} = 34.8\%$.

Plass reports a range of from 14 to 26 mgms. per 100 c.c. of blood plasma for the non-protein nitrogen in normal pregnancy. His ratio $\frac{\text{urea nitrogen}}{\text{non-protein nitrogen}}$ varies from 36 to 71 in the same cases.

The results of routine blood analyses carried out upon 53 patients in our clinic during the past year form the basis for this paper. In this series of analyses, we have studied conditions obtaining in normal gestation, as well as in the several toxemias of pregnancy, and in certain of the abnormal cases we have endeavored to obtain as many samples of blood for study from the same individual as was feasible. The findings in the cases of only a lim-

ited number of normal women are reported, as the results have been so consistently constant that a larger series seemed unnecessary.

### Methods

In all instances the blood samples were taken in the morning before breakfast and the whole blood was immediately subjected to analysis. Lithium citrate, in the proportion of 3 mgms. per c.c. of blood, was used as an anticoagulant. The non-protein nitrogen was determined by the Folin-Wu method, the blood-urea nitrogen by the Van Slyke-Cullen modification of the Marshall method, the uric acid by Folin's method, the chlorides by the Whitehorn method, and the $CO_2$ combining power according to Van Slyke's technique. All values are expressed in mgms. per 100 c.c. of blood, except the $CO_2$ combining power, which is given in volumes per cent.

We have used whole blood in the determinations for non-protein nitrogen, urea nitrogen, uric acid and chlorides. There seemed to be no advantage in using serum or plasma instead of whole blood for these analyses, as urea and uric acid tend to be in equal concentrations in the corpuscles and the surrounding fluid, while a definite relationship appears to hold between the non-protein nitrogen in the whole blood and that in the plasma. As soon as the blood was obtained from the patient, a Folin-Wu filtrate was made and all analyses were carried out immediately.

The results obtained from the analysis of 122 blood samples are given in the accompanying tables, in which the last column of figures represents the blood urea nitrogen expressed as a percentage of the non-protein nitrogen, $\frac{\text{U. N.}}{\text{N. P. N.}}$.

### NORMAL CASES.

TABLE I.

| No. | Date | N. P. N. | U. N. | Uric Acid | Chlorides | $CO_2$ | U. N. / N. P. N. | Remarks |
|---|---|---|---|---|---|---|---|---|
| 1 | 1/15 | 29.5 | 14.48 | 2.6 | 503 | 51.3 | 49.0 | Non-pregnant. |
| 2 | 1/18 | 30.9 | 16.81 | 3.1 | 500 | 58.1 | 54.4 | " " |
| 3 | 1/25 | 35.3 | 20.08 | 3.8 | 514 | 56.0 | 56.9 | " " |
| 4 | 1/25 | 33.0 | 19.15 | 3.7 | 514 | 46.6 | 58.0 | " " |
| 5 | 1,25 | 33.0 | 21.95 | 3.4 | 528 | 45.7 | 66.5 | " " |
| 6 | 1/16/24 | 29.1 | 14.01 | 2.1 | 536 | 44.7 | 48.2 | Pregnant at term. |
| 7 | 1/16/24 | 28.2 | 11.68 | 2.4 | 485 | 45.7 | 41.4 | " " " |
| 8 | 1/16 | 31.6 | 13.54 | 2.7 | 471 | 43.8 | 42.9 | " " " |
| 9 | 1/16 | 27.3 | 12.61 | 2.7 | 493 | 38.1 | 46.2 | " " " |
| 10 | 1/16 | 23.4 | 10.74 | 2.7 | 485 | 40.0 | 46.0 | " " " |
| 11 | 6/4 | 27 8 | 12.14 | 2.7 | 528 | 52.2 | 43.7 | " " " |
| 12 | 6/5 | 27.4 | 12.00 | 3.2 | 501 | 49.3 | 43.8 | " " " |
| 13 | 6/10 | 28.9 | 13.01 | 3.9 | 516 | 49.0 | 45.1 | " " " |

### NEUROTIC VOMITING.

TABLE II.

| No. | Date | N. P. N. | U. N. | Uric Acid | Chlorides | $CO_2$ | U. N. / N. P. N. | Remarks |
|---|---|---|---|---|---|---|---|---|
| 14 | 6/7 | 18.2 | 7.94 | | | 34.7 | 43.5 | Very mild case. |
| 15 | 9/6 | 26 4 | 16 81 | 4.8 | 478 | 44.7 | 63.7 | Severe case. |
| | 9/18 | 37.5 | 14.48 | 3.1 | 486 | 50.5 | 38.6 | Improved. |
| | 10/5 | 34.1 | 9.34 | 5.5 | 495 | 49.8 | 26.4 | Five days before discharge. |
| | 10/27 | 72.2 | 59.31 | 9.3 | 486 | 40.9 | 82.2 | Readmitted. |
| | 10/31 | 33.5 | 12.61 | 3.0 | 536 | 48.6 | 37.7 | — |
| 16 | 10/13 | 37.5 | 14.01 | 4.8 | 511 | 41.4 | 37.4 | — |
| | 10/16 | 27.3 | 9.34 | 3.7 | — | 43.3 | 34.2 | — |
| | 10/20 | 30.6 | 7.47 | 2.0 | 528 | 40.4 | 24.4 | — |
| | 11/1 | 26.8 | 11.21 | 2.3 | 544 | 45.3 | 41.8 | One day before discharge. |

### NEPHRITIC TOXEMIA.

TABLE III.

| No. | Date | N. P. N. | U. N. | Uric Acid | Chlorides | $CO_2$ | U. N. / N. P. N. | Remarks |
|---|---|---|---|---|---|---|---|---|
| 17 | 4/26 | 28.4 | 15.17 | | 400 | 50.3 | 53.4 | Mild case. |
| | 5/2 | 34.8 | 17.28 | | | 43.3 | 49.7 | |
| | 5/8 | 32.1 | 16.81 | | | 48.1 | 52.4 | |
| | 5/9 | 32.1 | | | | 48.2 | | |
| | 5/14 | 27.6 | 14.94 | | | 38.7 | 54.3 | |
| | 5/15 | 27 4 | 19 15 | | | 35.6 | 70.0 | Blood pressure rose and condition became worse just before delivery. |
| | 5/16 | 25.1 | 15.88 | 5.3 | | 41.4 | 63.1 | |
| 18 | 5/9 | 20.0 | 11.68 | 2.7 | | 58.4 | 53.8 | |
| | 6/8 | 18.7 | 11.68 | 5.6 | 544 | 62.4 | 45.3 | |
| | 6/15 | 27.7 | 11.21 | 5.6 | 546 | 40.6 | 55.1 | At term. |
| 19 | 5/16 | 29.1 | 17.75 | | | 57.4 | 61.0 | At term. |
| 20 | 5/8 | 28.2 | 14.94 | | | | 53.0 | At term. |
| | 5/9 | 28.2 | 11.8 | | | | 41.8 | |
| 21 | 6/11 | 28.0 | 13.54 | 4.9 | 511 | 50.1 | 48.5 | Mild case at term. |
| 22 | 11/1 | 30.9 | 14.94 | 4.2 | 503 | 45.7 | 48.5 | |
| | 11/15 | 30.3 | 16.35 | 5.3 | 495 | 48.1 | 54.0 | |
| | 11/26 | 28.5 | 20.55 | 4.7 | 488 | 44.8 | 72.0 | |
| | 11/29 | 31.6 | 20.78 | 3.8 | 496 | 48.9 | 65.7 | |
| | 12/13 | 36.1 | 15.88 | 3.7 | | 50.6 | 44.0 | After delivery and improved. |
| 23 | 10/23 | 26.2 | 14.48 | 3.7 | 518 | 42.4 | 55.4 | At term. |
| | 10/26 | 34.9 | 14.94 | 4.2 | 528 | 53.8 | 42.9 | |
| | 11/9 | 39 5 | 17.75 | 5.5 | 503 | 41.4 | 45.0 | |
| 24 | 11/21 | 37.7 | 14.01 | 3.5 | 529 | 39.5 | 37.2 | Mild case at term. |
| | 11/22 | 33.0 | 14.48 | 4.8 | 503 | 40.1 | 43.8 | |
| | 12/12 | 33.7 | 16.81 | 3.3 | 514 | 44.3 | 50.0 | |
| 25 | 12/31 | 60.0 | 37.83 | 6.7 | 471 | 38.5 | 63.2 | |
| | 1/2 | 58.8 | 44.36 | 6.9 | 491 | 39.5 | 75.1 | |
| | 1/12 | 68.3 | 28.02 | 6.7 | 508 | 46.2 | 41.1 | After delivery and improved. |
| 26 | 12/9 | 54.6 | 38.29 | 6.5 | 514 | 36.6 | 70.1 | |
| | 12/10 | 37.0 | 29.42 | 6.7 | 504 | 37.6 | 79.7 | |
| | 12/28 | 47.2 | 20.08 | 3.8 | 528 | 44.3 | 42.6 | After delivery and improved. |
| 27 | 9/25 | 37.5 | 25.22 | 3.3 | 462 | 40.0 | 67.4 | At term. |
| | 10/1 | 43.6 | 18.21 | 2.7 | 495 | 52.8 | 41.8 | |
| | 10/10 | 40.0 | 20.55 | 2.7 | 498 | 54.8 | 51.4 | |
| | 10/17 | 33.3 | | 4.9 | 511 | 54.8 | | |

TABLE III.—Continued.

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 28 | 4/28 | 40.0 | 25.22 | 5.5 | | 42.8 | 63.0 | At term. |
| 29 | 8/18 | 35.7 | 17.28 | | 462 | 41.4 | 48.3 | Mild case at term. |
| | 8/19 | 31.2 | 14.94 | 7.2 | 495 | 54.1 | 47.9 | |
| 30 | 12/4 | 33.0 | 19.61 | 3.6 | 514 | 47.1 | 59.5 | |
| | 12/14 | 33.7 | 16.35 | 2.7 | 478 | 41.4 | 48.5 | After delivery and improved. |
| 31 | 12/15 | 29.4 | 14.94 | 4.0 | 518 | 43.3 | 50.7 | Mild case. |
| | 12/28 | 30.0 | 11.21 | 6.1 | 513 | 42.4 | 37.4 | |
| | 1/2 | 39.5 | 18.60 | 4.7 | 508 | 33.8 | 47.1 | |
| | 1/10 | 37.2 | 13.54 | 4.1 | 491 | 54.8 | 36.4 | |

PRE-ECLAMPTIC TOXEMIA.

TABLE IV.

| No. | Date | N. P. N. | U. N. | Uric Acid | Chlorides | $CO_2$ | U. N. / N. P. N. | Remarks |
|---|---|---|---|---|---|---|---|---|
| 32 | 5/3 | 19.6 | 6.54 | | | | 33.3 | At term. |
| | 5/8 | 24.0 | 7.94 | | | | 33.0 | |
| | 5/16 | 26.8 | 12.14 | | | 31.9 | 45.4 | After delivery and improved. |
| 33 | 5/17 | 22.1 | 6.54 | 4.0 | | 50.0 | 29.5 | At term. |
| | 5/12 | 22.75 | 11.68 | | | | 51.3 | |
| | 5/25 | 28.4 | 10.27 | | | 45.5 | 36.2 | |
| | 6/9 | 22.8 | | 7.1 | 511 | 43.5 | | |
| 34 | 6/7 | 22.9 | 12.61 | | | 42.8 | 55.1 | |
| | 6/12 | 42.2 | 14.01 | 6.8 | 511 | 49.0 | 33.3 | At term. |
| 35 | 6/7 | 18.6 | 10.70 | | | 46.6 | 57.7 | Very mild case. Diagnosis not definite at term. |
| | 6/10 | 30.0 | | 5.4 | 512 | 42.3 | | |
| | 6/12 | 29.4 | 13.08 | 6.1 | 494 | 48.1 | 44.5 | |
| | 6/13 | 34.9 | 18.21 | 7.5 | 495 | 43.5 | 62.2 | |
| 36 | 8/28 | 115.3 | | 5.9 | 453 | 46.6 | | Diagnosis not definite at term. |
| | 8/30 | 38.9 | 23.82 | 6.0 | 446 | 50.4 | 61.4 | |
| | 9/4 | 35.7 | 25.22 | 4.5 | 528 | 49.4 | 70.6 | |
| | 9/13 | 38.5 | 20.55 | 5.3 | 515 | 42.4 | 53.2 | |
| | 9/28 | 28.2 | 7.94 | 4.0 | 528 | 50.8 | 28.2 | |
| 37 | 9/19 | 29.1 | 7.0 | 4.0 | 495 | 51.0 | 24.1 | |
| | 9/27 | 38.9 | 18.60 | 4.2 | 529 | 58.9 | 47.7 | After delivery and improved. |
| 38 | 9/20 | 53.6 | 13.54 | 4.2 | 478 | 42.8 | 25.3 | |
| | 9/25 | 54.6 | 24.75 | 6.8 | 530 | 42.8 | 45.3 | After delivery and improved. |
| | 10/6 | 34.5 | 16.35 | 5.7 | 528 | 50.8 | 47.4 | |
| | 10/13 | 43.2 | 20.08 | 4.0 | 528 | 56.2 | 46.4 | |
| 39 | 10/8 | 30.7 | 14.01 | 3.2 | 526 | 42.8 | 45.7 | Mild case. |
| | 10/12 | 40.0 | 20.08 | 4.6 | 518 | 52.3 | 50.2 | At term. |
| | 10/23 | 34.5 | 12.61 | 4.8 | 536 | 43.3 | 36.6 | |
| 40 | 10/17 | 35.3 | 14.01 | 8.3 | 511 | 45.3 | 39.8 | |
| | 10/20 | 39.5 | 17.75 | 3.6 | 511 | 48.5 | 44.9 | After delivery and improved. |
| | 10/27 | 30.6 | 15.88 | 2.6 | 528 | 50.8 | 51.9 | |
| 41 | 10/23 | 30.0 | 15.88 | 3.4 | 549 | 35.7 | 53.0 | Mild case. |
| | 10/27 | 34.3 | 17.75 | 3.3 | 528 | 41.4 | 51.7 | At term. |
| 42 | 10/26 | 29.3 | 12.14 | 5.3 | 561 | 41.4 | 41.4 | |
| | 11/11 | 36.4 | 15.41 | 3.8 | 510 | 45.3 | 42.4 | |
| | 11/21 | 34.9 | 12.61 | 4.0 | 529 | 45.3 | 36.2 | |
| 43 | 10/26 | 30.6 | 14.01 | 4.4 | 544 | 53.8 | 45.9 | At term. |
| 44 | 12/9 | 50.4 | 21.95 | 4.3 | 501 | 40.6 | 43.6 | Diagnosis not definite at term. |
| | 12/10 | 34.3 | 19.61 | 5.3 | | 38.0 | 57.2 | |
| | 12/12 | 36.3 | 21.48 | 4.7 | 471 | 48.4 | 59.2 | |
| | 12/19 | 34.5 | 12.61 | 4.2 | 478 | 36.6 | 36.6 | |
| 45 | 1/18 | 33.7 | 11.68 | | 510 | 46.6 | 34.7 | At term. |

ECLAMPSIA.

TABLE V.

| No. | Date | N. P. N. | U. N. | Uric Acid | Chlorides | $CO_2$ | U. N. / N. P. N. | Remarks |
|---|---|---|---|---|---|---|---|---|
| 46 | 6/1 | 26.3 | 9.34 | 11.9 | 544 | 40.3 | 35.5 | Severe at term. |
| | 6/3 | 21.8 | 9.81 | 18.0 | 511 | | 43.1 | |
| 47 | 6/9 | 45.0 | 18.21 | | 478 | 40.7 | 40.6 | Mild after delivery |
| 48 | 6/13 | 35.3 | 14.94 | 5.6 | 544 | 39.0 | 42.3 | Mild after delivery |
| 49 | 8/24 | 29.1 | 14.01 | | 495 | 38.5 | 48.2 | Mild after delivery |
| | 8/25 | 34.9 | 17.75 | 5.0 | 495 | 45.7 | 50.8 | |
| 50 | 11/30 | 32.6 | 22.42 | 6.2 | 495 | 20.2 | 68.9 | After delivery. |
| | 12/1 | 40.6 | 28.49 | 7.2 | 488 | 35.2 | 70.0 | |
| | 12/8 | 35.9 | 24.75 | 5.5 | 496 | 47.1 | 69.0 | |
| 51 | 1/3 | 34.7 | 14.01 | 4.9 | 471 | 45.3 | 40.4 | At term. |
| | 1/18 | 40.0 | 20.55 | 4.0 | 465 | 50.4 | 51.3 | Improved. |
| 52 | 1/19 | 32.6 | 12.14 | 5.8 | 508 | 43.8 | 37.3 | Immediately after delivery. |
| | 1/24 | 45.0 | 16.81 | 3.1 | 516 | 50.8 | 37.4 | Improved. |
| 53 | 1/22 | 28.0 | 15.41 | 9.0 | 562 | 32.8 | 55.0 | After delivery. |

*Normal Cases.*—Our studies show that in the normal non-gravid woman the non-protein nitrogen ranges from 29.5 to 35.3 mgms. per 100 c.c. of blood with an average of 32.3; the urea nitrogen varies between 14.48 and 21.95 mgms. per 100 c.c. of blood, with an average of 18.5, while the ratio $\frac{\text{urea nitrogen}}{\text{non-protein nitrogen}}$ lies between the limits 49.0 and 66.5, with an average of 57. The uric acid is approximately 3.3 mgms. per 100 c.c. of blood, and the $CO_2$ combining power about 52 volumes per cent.

In normal pregnant women we note a definite tendency toward lower values in both the non-protein nitrogen and the urea nitrogen, the averages being 28 and 12.48 mgms. per 100 c.c. of blood, respectively, as compared with 32.3 and 18.5 mgms. in the non-pregnant woman. The ratio $\frac{\text{urea nitrogen}}{\text{non-protein nitrogen}}$ is also definitely lowered, ranging between 41.4 and 48.2 and averaging 44.7, instead of 57. The uric acid is about 2.8 mgms. per 100 c.c. of blood, while the $CO_2$ combining power has decreased from an average of 52 in the non-gravid to 45 volumes per cent, thereby clearly demonstrating the existence of the so-called "acidosis of pregnancy." Throughout the tables the chloride content varies within very narrow limits in the several conditions, 471 to 536 mgms. per 100 c.c. of blood.

*Neurotic Vomiting of Pregnancy.*—The mild cases of neurotic vomiting show no disturbance in the blood chemistry. When, however, the patient has vomited persistently for a week or longer marked disturbances in the ratio $\frac{\text{U. N.}}{\text{N. P. N.}}$ occur. The patient, designated as Case 15, Table II, was admitted to the hospital in a very bad condition, with an $\frac{\text{U. N.}}{\text{N. P. N.}}$ ratio of 63.7. When she was

discharged as cured two weeks later, this ratio had fallen to 26.4. Following this the condition recurred and three weeks later she was readmitted to the hospital vomiting persistently and greatly emaciated. At that time the ratio $\frac{U.N.}{N.P.N.}$ had risen to 82.2; she was again treated and, when she was discharged at the end of a week, the ratio had fallen to 37.7. Moreover, it is also interesting to note that our tables show that as the ratio $\frac{U.N.}{N.P.N.}$ increases, there is a corresponding rise in the uric acid content of the blood, which in one instance rose as high as 9.3 along with a decrease in the $CO_2$ combining power.

*Nephritic Toxemia.*—As would be expected, there is a definite increase in the non-protein nitrogen, the blood urea nitrogen and the uric acid in the nephritic type of toxemia; and this increase is fairly proportional to the severity of the condition. What is perhaps of more interest is that the ratio $\frac{U.N.}{N.P.N.}$ also increases with the severity of the disease; whereas, when the patient improves, due either to delivery or rest in bed with suitable dietetic treatment, it returns to a normal figure. On the other hand, the $CO_2$ combining power is only very slightly lowered, except in extremely severe cases.

*Pre-eclamptic Toxemia.*—Investigations now in progress in this clinic indicate conclusively that the condition clinically diagnosed as pre-eclamptic toxemia is not always a definite entity. As the subsequent course of these patients is followed, after they leave the hospital, it is possible to divide them into two groups:—those who present signs and symptoms of chronic nephritis, and those who do not; and it seems justifiable to designate only the latter as true pre-eclamptic toxemia. In Table IV, a marked increase in the ratio $\frac{U.N.}{N.P.N.}$ comparable to that of the nephritic type, is noted only in those cases in which the diagnosis was not definitely established. Ruling out these cases, we must conclude that in pre-eclamptic toxemia the ratio $\frac{U.N.}{N.P.N.}$ is not increased, but rather tends to present a low value. As the patient improves, the ratio rises to within the normal limits. The non-protein nitrogen and the $CO_2$ combining power stay fairly within the normal range; while there is a slight increase in the uric acid content of the blood in this type of toxemia.

*Eclampsia.*—The non-protein nitrogen figure is not greatly altered in eclampsia, but we note, however, a change in the urea nitrogen and the uric acid. Thus, in all the analyses recorded in Table V, except those of Case 50, there is a decrease in the urea nitrogen, giving a low $\frac{U.N.}{N.P.N.}$ ratio. The figures are similar to those noted in the definitely pre-eclamptic patients. It is quite possible that there is an underlying nephritic condition in Case 50, judging from the patient's past history and the microscopic picture of her urine. In eclampsia the uric acid content is markedly increased, while the $CO_2$ combining power remains fairly normal, and thus afford no basis for the belief in an increased acidosis.

## Conclusions

1. The normal non-pregnant woman has approximately 32 mgms. of non-protein nitrogen, 18.5 mgms. of urea nitrogen and 3.3 mgms. of uric acid per 100 c.c. of blood, with a $CO_2$ combining power of the blood plasma of about 52 volumes per cent.

2. In normal pregnancy the non-protein nitrogen, as well as the urea nitrogen content is less than in the non-pregnant woman, the averages being 28 and 12.48 mgms. per 100 c.c. of blood, respectively. The uric acid is about the same as in the non-gravid person, while the $CO_2$ combining power drops from 52 to 45 volumes per cent. The ratio $\frac{U.N.}{N.P.N.}$ is also decreased, being about 44.5 as against 57 in the non-pregnant woman.

3. In neurotic vomiting our figures show an increased value for the non-protein nitrogen and uric acid in the fairly severe cases. These return to within normal limits as the patient improves.

4. The non-protein nitrogen tends to increase in nephritic toxemia and to an extent fairly proportional to the severity of the condition; whereas, in the definitely pre-eclamptic type of toxemia, this tendency is not so striking, The ratio $\frac{U.N.}{N.P.N.}$ is definitely increased in the nephritic, while it is either normal or decreased in the pre-eclamptic type.

5. In true eclampsia fairly normal values are found for the non-protein nitrogen and the $CO_2$ combining power. The ratio $\frac{U.N.}{N.P.N.}$ is similar to that found in pre-eclamptic toxemia.

6. The uric acid content of the blood is definitely elevated in all three types of toxemia, nephritic, pre-eclamptic and eclamptic.

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# ATYPICAL DISTRIBUTION OF VARICELLA LESIONS DEPENDENT UPON A COEXISTENT SYPHILITIC INFECTION

## REPORT OF A CASE

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The distribution of the lesions is frequently just as important a factor in the diagnosis of skin eruptions as the character of the individual lesions. Therefore, when the distribution of the skin lesions is atypical of the disease suspected, the question of a differential diagnosis or of an interpretation of the unusual distribution immediately arises. Although chicken-pox, one of the eruptive fevers, is a general infection, the chief and often the only manifestation of the disease is the appearance of more or less characteristic skin lesions which are, for the most part, diffusely distributed over the trunk and to a less extent over the scalp, face and extremities (Fig. 1). Not infrequently, however, the lesions are most numerous over parts of the body usually least involved or are clustered over small areas of the body out of proportion to the general distribution. When these variations in the usual distribution of the lesions occur, chicken-pox is most frequently confused with small-pox or herpes zoster. Occasionally, variations in the skin eruptions of diseases, not usually confused with chicken-pox, cause difficulty in arriving at a correct diagnosis. Hereditary syphilis is one of these diseases. The lesions of hereditary syphilis are usually macular, papular or pustular and are most numerous over the face, around the buttocks and over the extremities (Fig. 2). In young, severely infected, infants, however, the lesions may be bullous, and when this occurs, the disease is spoken of as *pemphigus syphilitica*. When the infection of the infant is slightly less severe, the individual lesions may be clear vesicles, and although distributed differently from the lesions of varicella, they resemble them so closely macroscopically that the disease under these conditions is spoken of as *varicella syphilitica*.

Irritation has a direct influence on the localization of the virus of varicella in the skin, as evidenced by the appearance of an unusual number of vesicles at the site of irritation. The abnormal distribution of the lesions of chicken-pox can usually be explained by the presence of a preexisting or of a coexisting skin irritation. This phenomenon was discussed in a preceding paper [1] and instances were given in which the distribution of varicella lesions was influenced in this way. The object of the present paper is to report a case of varicella in which the unusual distribution of the lesions was dependent upon the irritation of the skin by a coexistent disease, hereditary syphilis.

### REPORT OF CASE

Patient: R. A., Female, aged 7 mos. Admitted: December 7, 1923.

*Chief Complaint:* Skin eruption.

*Family History:* The patient's mother was admitted to one of the hospitals of the city on April 10, 1923, with a diagnosis of toxaemia of pregnancy. The child was born, at normal term, May 3, 1923. There was no evidence of syphilis in the child or in the mother at that time.

*Past History:* On May 22, 1923, the child was admitted to one of the hospitals of the city, with a diagnosis of gonorrheal ophthalmia and malnutrition. The ophthalmia cleared up under treatment, but the general condition of the child did not improve. A diagnosis of nasal diphtheria was made on July 26th. The diagnosis was verified in the usual way by means of cultures. A complete recovery followed the administration of antitoxin as evidenced by the disappearance of

symptoms and by cultures negative for diphtheria bacilli on August 3rd and September 3rd. On November 21, the baby acquired an acute respiratory infection which was diagnosed influenza and from which she was supposed to be recovering at the time of admission to this hospital.

*Present Illness:* During the afternoon of December 6th, the day before admission, the patient developed, without prodromal symptoms, a slight increase in fever. Papules and vesicles appeared on her face and buttocks. A diagnosis of varicella was made and the child was transferred to the Hospital of the Rockefeller Institute on December 7th.

*Exposure:* The patient was removed from a ward in which other cases of varicella were occurring at the same time. Three of these patients, showing varicella typical in every respect, had been transferred to this hospital only a few days previously.

*Physical Examination on Admission:* Temp.: 101° F. Pulse: 138 per min. Res.: 38 per min.

*General Appearance:* The patient is an undernourished and undersized infant who appears to be acutely ill. She breathes with difficulty and makes a noise suggesting snuffles. The voice is almost completely lost, and only a hoarse wheezing sound is heard when the baby cries.

*Head:* The shape of the head is normal. The posterior fontanelle is closed. The anterior fontanelle is open but does not bulge.

*Eyes:* The pupils are equal and react to light. There is no interstitial keratitis. A conjunctivitis with a purulent discharge is present.

*Nose:* A bloody nasal discharge is present which forms a thick, brownish crust, almost entirely occluding the nasal orifices. Removal of the crust exposes a raw, bleeding surface.

*Ears:* Superficial and otoscopic examinations of the ears are negative.

*Throat:* The tonsils are large and inflamed. Pus is present in the crypts but no definite membrane is seen.

*Chest:* Inspiration is normal. Expiration is prolonged and forced, owing to an obstruction in the upper respiratory tract. The lungs are resonant throughout to percussion and clear vesicular breathing is heard on auscultation.

*Heart:* The heart is not enlarged. The heart sounds are normal and no murmurs are heard.

*Abdomen:* The abdomen is symmetrical, soft, and slightly protruding. A smooth firm spleen, with a well-defined edge, extends 3 cm. below the costal margin. The edge of a smooth, firm liver is felt 4 cm. below the costal margin.

*Glands:* The inguinal, axillary, epitrochlear, anterior, and especially the posterior cervical lymph glands are enlarged and firm.

*Bones:* At the middle of the shaft of the left humerus a hard callus-like protrusion is felt on the internal surface. The bone is fixed and is not painful when touched or moved. The right femur presents a similar deformity about the middle of the shaft.

*Skin:* The skin is dry, wrinkled, and slightly brawny. An eruption is present which is characterized by three types of lesions: papules, vesicles, and pustules. The predominating type is vesicles. The eruption is distributed over the scalp, face, neck, buttocks, thighs, and to a less extent over the upper extremities and legs. Only four lesions are seen on the trunk, three papules in the interscapular region and one on the left nipple. Except for a predominance of pustules in the scalp and a scattering of papules over the buttocks and extremities, the eruption consists of vesicles. The vesicles are discrete, clear, thin-walled, superficial, with crenated edges, and of a uniform pea size. The pustules of the face and scalp are similar to the vesicles in size and shape, but have an areola of redness which is not seen around the vesicles. The papules vary in size from pinhead to the dimensions of the vesicles. While the character of the individual lesions is typical of varicella, the distribution is atypical.

*Summary of Positive Findings:* Conjunctivitis with a purulent discharge, rhinitis with a membrane, tonsillitis without a membrane, enlargement of the spleen and liver, general glandular enlargement, bone deformities, skin eruption and malnutrition are the most important findings revealed by the physical examination of the patient on admission to the hospital.

*Laboratory Examinations:* Only Gram-positive cocci were seen in stained films of the conjunctival pus, from which *Staphylococcus aureus* and *Streptococcus hemolyticus* were recovered by means of cultures on blood agar plates. Many Gram-positive bacilli, morphologically like *B. diphtheriae*, were seen in stained films of the nasal discharge. Diphtheria bacilli, which were subsequently shown to be virulent for guinea pigs, were isolated from the nasal discharge by means of cultures on Loeffler's blood serum, and blood agar plates. Virulent diphtheria bacilli were also recovered from the throat in a similar manner.

*Blood Wassermann:* + + + + positive.

*X-Ray:* Old fractures, middle third of left humerus, middle third of right femur, and upper third of left ulnar. Periostitis, involving the long bones of the extremities.

*Course in the Hospital:* December 8th: During the past 24 hours the patient's temperature rose to 103°F. The nose presents the same thick, brownish, hemorrhagic exudate which almost entirely occludes the nasal orifices. A laryngologist reports that no membrane is present in the larynx. Diphtheria antitoxin, 20,000 units, is administered intramuscularly.

There is an increase in the number of skin lesions in the areas already involved, namely, the scalp, face, buttocks and thighs. Some of the vesicles on the buttocks are beginning to soften and wrinkle. Papules and vesicles are also appearing on the arms, legs, palms and soles, parts of the body previously not at all or only slightly implicated.

*December 9th:* The patient's temperature has risen to 104.5°F. This rise is probably due, in part at least, to a reaction following the administration of the antitoxin. There is a continued increase in the number of vesicles over the legs, arms, palms and soles. The trunk, however, remains free from lesions. New and old lesions are seen adjacent to each other; the new vesicles are just appearing, while those of a previous "crop" are beginning to dry. Many of the vesicular lesions, especially over the scalp and face, are becoming pustular. *Staphylococcus aureus* was recovered from these pustules by means of cultures on blood agar plates.

*December 10th:* The temperature has dropped to 102°F. The general condition of the baby is much improved. The nasal discharge is decreasing and the patient breathes easily when asleep. The purulent conjunctivitis has almost entirely cleared up following irrigations with boric acid solution. No new skin lesions are seen and those present are either drying or becoming pustular.

*December 17th:* During the past seven days the patient has continued to improve. Although the nasal discharge is less copious and the obstruction in the nose has almost entirely disappeared, the snuffles still persist. The vesicles, not secondarily infected, quickly formed dry scabs which dropped off in a few days. Many of the lesions, which became secondarily infected with pyogenic cocci, however, are still present and are filled with yellowish pus or covered by thick scabs. Throughout the course of the chicken-pox eruption, the baby's trunk remained practically free of lesions, while the arms, legs, palms, soles, face and scalp were covered with lesions (Figs. 3 to 5). More lesions occurred on the extensor than on the flexor surfaces of the extremities.

Fig. 1

Fig. 2

Fig. 3

Fig. 4

Fig. 5

Fig. 6

### DISCUSSION

The presence of congenital syphilis, suspected on account of the persistent snuffles, enlarged spleen and liver, general glandular enlargement and periostitis, was confirmed by a positive blood Wassermann. These findings suggested the possibility that the skin eruption might be syphilitic. The idea that the eruption in this case was due to syphilis was immediately abandoned, however, because the vesicular and bullous types of cutaneous syphilis occur in severely infected infants at birth or shortly afterwards. Furthermore, the lesions are usually much larger or more deeply seated than varicella vesicles, present slow transitory stages and are followed by a coppery discoloration in the skin involved. The diagnosis of varicella in this case was substantiated by the definite history of exposure to chicken-pox, the age of the patient, the superficiality of the individual lesions, the occurrence of the lesions in "crops" presenting all stages of development simultaneously, and recovery of the patient in some 12 or 14 days without anti-syphilitic treatment.

Although authors of textbooks on skin diseases and childrens' diseases differ somewhat in their descriptions of the distribution of the cutaneous manifestations of congenital syphilis, most of them agree that the eruption is least marked over the trunk (Fig. 2). Holt [2] says, "It is usually most abundant about the center of the face, the extensor surfaces of the upper and lower extremities, and especially the hands and feet." Conner [3] describes it as being "most abundant over the face, neck and buttocks, extensor surface of the extremities, and the palms and soles" (Fig. 2). The unusual distribution of the lesions in the case of varicella reported in the present paper corresponds closely to the usual distribution of the lesions in congenital syphilis; hence the coincidental occurrence of the two diseases in our patient suggests that the unusual distribution of the varicella lesions was dependent in some way upon the coexistent syphilitic infection.

The distribution of the eruption of many of the exanthemata is directly influenced by irritation of the skin. An especially abundant eruption (Fig. 6) is frequently seen on parts of the body which have been affected by mechanical or chemical irritation before or shortly after the appearance of the exanthem. Von Pirquet [4] and Schick [5] have demonstrated this phenomenon in measles, Swoboda [6] and Rivers and Tillett [1] in varicella, and Hebra,[7] Tièche,[8] and many others, in smallpox. Calmette and Guérin [9] have shown that vaccine virus injected intravenously into rabbits can be made to localize in the skin if certain areas be injured immediately after the injection by shaving or pulling out the hair.

It has been known for a long time that mechanical and chemical irritation of the skin will alter the distribution and configuration of certain skin eruptions. At present we wish to emphasize the fact that a coexistent disease may also influence the distribution of the lesions of certain infectious diseases. It is not known whether this influence is entirely dependent upon the irritation produced by the coexistent disease or whether other factors are involved in the phenomenon. In a previous paper [1] we reported a case of varicella in which the distribution of the lesions was atypical, owing to the presence of a severe acne over the face and upper part of the back. The varicella lesions were most marked over these areas and actually involved the acne lesions. Denney and Hopkins [10] and Hasseltine [11] recently reported that lepers are unusually susceptible to vaccine virus, as evidenced by a very severe reaction at the site of the vaccination and also by an acute exacerbation of the leprous lesions throughout the body. None of their cases, however, was permanently aggravated by vaccination and some actually appeared to be improved after the subsidence of the reaction following the vaccination. The former observers [10] say: "A symbiotic relation existing between vaccine virus and the bacillus of leprosy offers the best explanation of the phenomena observed." It is difficult to determine from their report whether they believe that the vaccine virus invaded the blood stream of the patients and subsequently localized in the parts of the body irritated by the leprosy lesions. We believe that vaccine virus enters the blood stream of the majority of individuals who are vaccinated and that it manifests itself over parts of the body remote from the site of the primary inoculation only when the individuals are unusually susceptible to the virus or when parts of the body have been previously irritated in some manner. This belief is substantiated by the work of Ohtawara [12] and Rivers and Tillett,[1] who have demonstrated that vaccine virus can be recovered from the blood of rabbits vaccinated on the skin, and by the work of many observers who have shown that vaccine virus injected into rabbits intravenously localizes in areas of the skin previously irritated by shaving.

The case reported in the present paper is an example of the influence which one disease may have on the distribution of the lesions of another occurring simultaneously in the same patient. In this instance congenital syphilis altered the distribution of the varicella lesions. Although there is no history of a syphilitic eruption in our patient, the unusual occurrence of the varicella lesions over parts of the body usually implicated in congenital syphilis seems to indicate that syphilitic lesions were present or had been present over these areas and had caused sufficient irritation to influence the localization of the varicella virus.

### SUMMARY

A case of varicella is reported in which the eruption was most marked over the face, scalp and extremities instead of over the trunk. The unusual distribution of the lesions in this case is believed to have been dependent upon a coexistent syphilitic infection.

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LEGENDS

Fig. 1.—Photograph of a case of varicella showing the usual distribution of the lesions.

Fig. 2.—Photograph of a case of congenital syphilis showing the usual distribution of the lesions. (By courtesy of J. B. Lippincott Company from an article on syphilis by Hochsinger in Pfaundler and Schlossmann's *Diseases of Children*, English edition, 1912.)

Fig. 3.—Photograph of the patient showing the varicella lesions over the face and extremities. The trunk is not implicated. The picture was made on the tenth day of the disease and most of the lesions seen are the ones which became secondarily infected.

Fig. 4.—Flexor surface of the right arm of the patient. Very few lesions are seen.

Fig. 5.—Extensor surface of the right arm of the patient showing numerous lesions. Compare this picture with Fig. 4.

Fig. 6.—Photograph showing the influence of irritation upon the distribution of the eruption of varicella. The irritation in this case was produced by the baby's napkin which was not changed frequently enough. Two other children in the same family also had chicken-pox, one simultaneously with the patient, the other a fortnight previously. All of these children were patients in the Rockefeller Hospital.

# THE EFFECT OF METHYL GUANIDINE ON THE BLOOD PRESSURE

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The probable presence of some substance in the urine capable of exercising a profound influence on the blood pressure has been discussed and studied by numerous investigators. It is evident that any product of metabolism able to produce a striking rise in the blood pressure, could, if not excreted properly, induce very marked changes. Many writers have suggested that such a substance may be responsible for the high blood pressure observed in essential hypertension, in chronic nephritis and in allied conditions, such as eclampsia.

During the past few months we have been studying the effects of certain of the non-protein nitrogen substances upon the blood pressure. While creatinine and creatine have appeared inert, certain derivatives and closely allied substances have shown marked pressor effects. The results obtained with methyl guanidine have been so constant and so striking, that a brief report of these experiments will be made.

Kutscher and Lohmann [1] first described the presence of methyl guanidine in the urine of normal individuals. Achelis [2] described its presence in the urine of the dog, horse and man, and pointed out that, although the horse eats no creatinine, he excretes considerable quantities of methyl guanidine. He also noted that the subcutaneous injection of methyl guanidine produced no appreciable increase in the amount of methyl guanidine excreted. Engeland [3] demonstrated the presence of dimethyl guanidine in the urine.

Koch [4, 5] noted the presence of guanidine compounds in the urine of dogs which had been subjected to parathyroidectomy. Noel Paton and Findlay [6] described an increased urinary output of guanidine compounds in tetania parathyreopriva and in idiopathic tetany, and Findlay and Sharpe [7] and Nattrass and Sharpe [8] found an increased excretion of dimethyl guanidine in idiopathic tetany. Sinalnicoff and Bovshik,[9] in a brief summary, describe a pressor effect of dimethyl guanidine, and their results resemble ours closely.

In our experiments dogs were anesthetized with ether and the carotid connected with a writing mercury manometer in the usual manner, methyl guanidine nitrate and methyl guanidine sulphate were used, and in the first set of six experiments these compounds were injected into the femoral vein. The animals were kept under anesthesia until the conclusion of the experiment.

A tracing was first obtained, and as soon as the blood pressure became constant, 0.1 gm. per kilo of body weight was injected. This injection produced at first a slight fall in blood pressure, followed within a minute by a sharp rise, then a more gradual rise reaching its maxi-

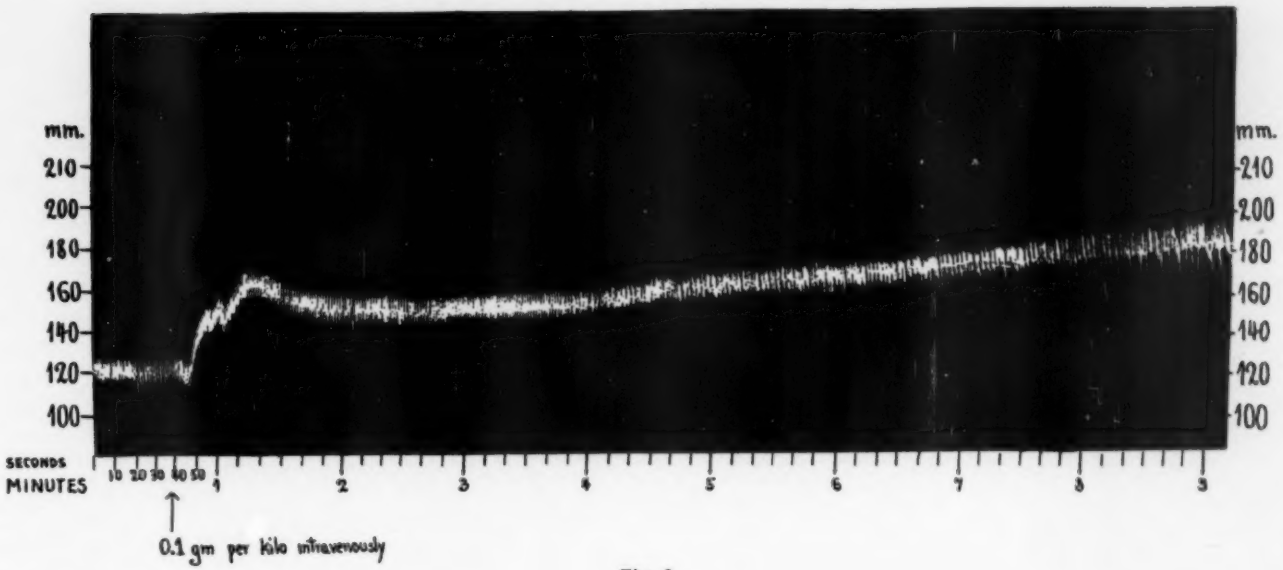


Fig. I.

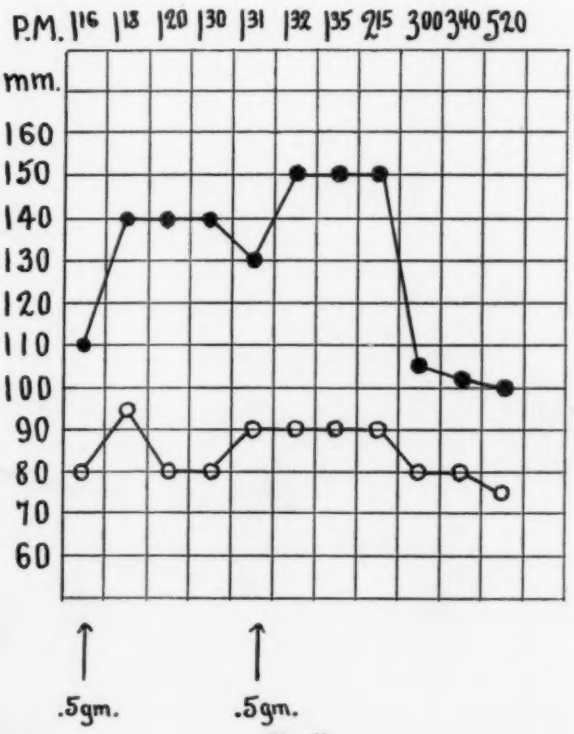


Fig. II.

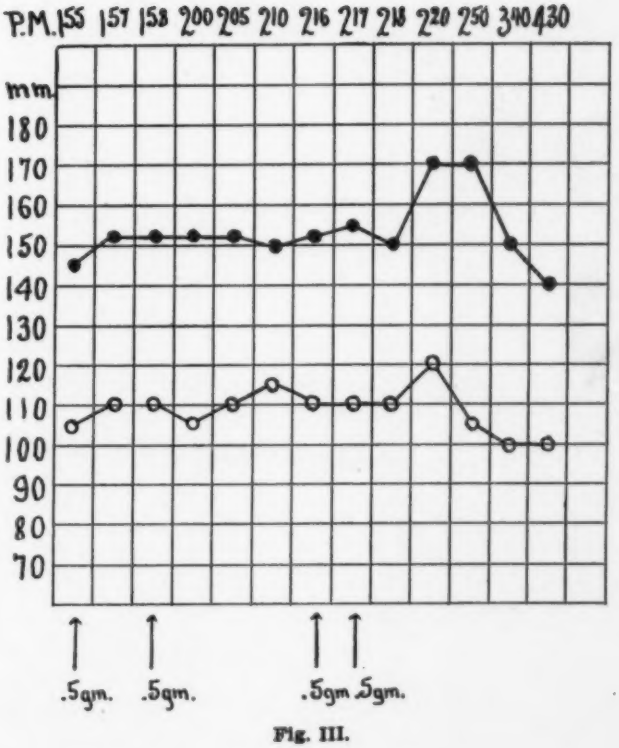


Fig. III.

mum in from ten to twenty minutes (Fig. 1). The average blood pressure before injection was 120 mm.; the average maximum following the first injection was 180 mm. At the end of one-half hour the same dose was repeated, and this was followed again by a rather rapid rise in blood pressure, the average maximum attained being 210 mm.

Just as striking as the prompt rise was the persistence of a high blood pressure, the second maximum being maintained until shortly before death. One animal with a blood pressure of 120 mm. showed, following the two injections, a blood pressure of 240 mm. which was maintained for four hours without any subsequent injections.

Some of the animals before death showed slight convulsive twitchings of the legs and face, but the rise in blood pressure occurred in all cases at least one hour before these twitchings appeared. This indicates that the pressure-raising effect was independent of even mild convulsions. The heart beat following injection was stronger, the apex impulse more forcible and the pulse somewhat slower, the average decrease in the rate being twenty per minute.

Section of both vagi produced no increase in the heart rate and no change in the blood pressure as previously noted by Sinalcinoff and Bovshik (*l. c.*). This points to a powerful vaso-constrictor effect of methyl guanidine as the most probable cause of the marked hypertension.

Four animals were injected with 0.2 gm. of methyl guanidine sulphate per kilo body weight intramuscularly, and blood pressure tracings taken. In these animals a marked and sustained rise in blood pressure also occurred, but it did not appear until twenty minutes after injection.

It was noted that, in the animals which received a lethal dose, respiration ceased before the heart beat. When artificial respiration was employed, it was possible to keep the animals alive half an hour or more before the heart ceased beating.

Several records of the effect of methyl guanidine upon the blood pressure in man were obtained. The substance was injected intravenously in doses varying from .045 gm. to .08 gm. per kilo. No unpleasant symptoms, aside from a sense of slight fullness in the head and a slight pounding of the heart, were noted. The systolic and diastolic blood pressures were promptly elevated and these elevations persisted for one hour. The systolic blood pressure was elevated in these observations from 30 to 50 mm., and the diastolic pressure from 15 to 20 mm. Two of these curves are shown in Figs. 2 and 3.

### DISCUSSION

The ability of methyl guanidine, a product of metabolism, to produce such a marked and sustained rise of blood pressure, is of considerable interest. It seems possible that this substance, if produced in excess in the body, or if not excreted by the kidneys, might cause a rise of blood pressure.

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### LEGENDS

Fig. 1.—Effect of methyl guanidine upon the blood pressure of dog. Note rise in blood pressure from 120 to 185 in nine minutes.

Fig. 2.—Effect of methyl guanidine upon the blood pressure in man. .045 gm. per kilo body weight. Systolic pressure in solid dots, diastolic pressure in hollow circles.

Fig. 3.—Effect of methyl guanidine upon the blood pressure in man. .08 gm. per kilo body weight. Systolic pressure in solid dots, diastolic pressure in hollow circles.

# CHANGES IN THE HUMAN OVIDUCT DURING THE MENSTRUAL CYCLE AND PREGNANCY

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### INTRODUCTION

In a histological description of the pig's oviduct, published recently (Snyder, 1923), it was shown that the successive stages of the oestrous cycle are marked by clear-cut histological changes in the tubal epithelium by which the period of oestrus can be distinguished from the interoestrous interval. Moreover, it was possible to recognize a characteristic state of the epithelium which

is found only about the time when the ova are in transport through the tubes. Great interest is attached to these facts because they are in accord with our growing knowledge of those periodic changes in the ovaries, uterus, and vagina which form the anatomical expression of the reproductive cycle in mammals.

For this reason it has seemed worth while to undertake a similar study of the human Fallopian tubes throughout the menstrual cycle. Certain preliminary observations upon the human tube, made in the light of the writer's studies on the pig, showed a greater similarity in detail between the two species than might have been expected on the basis of current textbook descriptions. Should this resemblance of structure be accompanied by more or less functional similarity as regards cyclic changes in the epithelium, we might thus have an opportunity to compare the known ovarian cycle of the pig (as reflected by changes in the tubal epithelium) with the almost unknown human cycle, and thus to estimate, indirectly, the time of ovulation in the menstrual cycle. Efforts to form such an estimate by comparison of cyclic changes in the human uterus with those in other animals have been frustrated by the relatively great cyclic and structural dissimilarity between the uteri of various mammalian species; but it is obvious that both in structure and function the oviducts are relatively constant in all mammals, and therefore may be susceptible of direct comparison.

In previous observations interest has centered largely on the epithelial lining of the tubes, particularly its structural changes during the reproductive cycle, and the factors in the transport of the ova through the tubes. In 1886, Frommel distinguished in man and in some of the lower animals the non-ciliated cells and described their resemblance to secretory epithelium in contrast to the adjacent ciliated cells. Since then a periodic variation in the morphology of the tubal epithelium, involving the alternation of a ciliated and a non-ciliated (secretory) phase, has been described in the human by Schaffer and Tröscher, and in the rabbit, pig, and other animals by Moreaux, Katz, Schaffer, and Gianelli. These investigators, however, in selecting specimens to represent all stages of the cycle, were handicapped by an inadequate knowledge of the ovarian and uterine cycles. In general, they have emphasized the importance of the cilia in the transport of the ova through the tubes and have held that during oestrus and pregnancy, as well as during menstruation in the human, the ciliated cells are diminished in number, and the non-ciliated cells, which appear to be secretory, are increased. As Schaffer has summarized it, "the secretory or gland cells are not elements *sui generis*, but arise from the ciliated cells, due to far-reaching alterations consequent to change in function."

In the tubes of the mouse, Allen (1922, p. 335) has described cyclic changes in which a loss of cilia from some of the ciliated cells is followed by extrusion of their nuclei into the lumen of the tube, the extrusion of nuclei in the ciliated portion beginning in the early metoestrum and continuing in a marked degree sometimes to the middle of the following pro-oestrum. The rôle of the cilia and the clinical hypotheses which have followed the above-mentioned observations have been discussed previously (Corner and Snyder, 1922; Keye, 1923; Seckinger, 1923).

Czyzewicz (1908), in six specimens selected especially for a study of the human tubes at menstruation, found "no blood or anything else passing from the epithelium."

It is evident that the value of the specimens of tubes as representative of the various phases of the menstrual cycle is increased in proportion to the anatomical evidence at hand as to the stage of the cycle, such as is obtained, for instance, by examination of the uterine mucosa or by recovery of the ovum while in transit through the tube. A detailed history of the menstrual cycles from puberty is also important, especially if sufficient data be obtained to exclude those cases which seem abnormal. Fuller application of available technical methods in the attempt to recover the ovum in transit (Corner, 1923) and observations on the contractions of the tubal musculature and ciliary activity obviously necessitate examination *in vivo*.

## Method and Material

The present investigation marks an attempt to observe the human Fallopian tubes at various phases of the reproductive cycle and in pregnancy. Through the generosity of Dr. Thomas S. Cullen and Dr. J. Whitridge Williams, free access was had to the extensive material of the gynecological and obstetrical laboratories of the Johns Hopkins Hospital, including valuable histological preparations and complete records. It was thus possible to collect 75 tubes, 62 from the non-pregnant and 13 from the pregnant. The series was chosen from a large number of specimens as the most favorable, the selection being made primarily on the basis of absence of obvious pathological changes on microscopical examination, and a history which showed no marked abnormality of the menstrual cycles from puberty. For instance, specimens were excluded in which there was a history of intermenstrual bleeding or of irregularity in the recurrence of the cycles, such as at the menopause. The case records contained definite notes as to the age, race, past history of illness, age of onset of menstruation, regularity of recurrence, duration, symptoms, amount of flow, date of onset of the last period and of the preceding one, occurrence of intermenstrual bleeding, marital history, date of operation and report of pathologist on tissues removed.

Since a great majority of the specimens were obtained from operations in cases of myomata uteri, in not a few instances the uterine mucosa, as well as the tubes, was at hand. In 18 of the 62 non-pregnant cases the endome-

trium, with at least a small area of the surface epithelium intact, was available in histological preparations. Thus it was possible to compare the state of the tubal epithelium with the coincident changes in the uterine mucosa. Upon the basis of this anatomical evidence, correlation could be established between the structural state of the tubes and the various phases of the menstrual cycle. In the 13 specimens obtained during pregnancy there were anatomical findings diagnostic of pregnancy. Correlation of the structural state of the tubes with the various phases of the menstrual cycle and pregnancy is based, therefore, upon anatomical evidence as to the state of the uterus in 31 cases, 18 non-pregnant and 13 pregnant.

The changes in the ovaries could be compared with the coincident condition of the tubal epithelium and endometrium during the cycle in two cases in which there was a section from the ovary showing a recent corpus luteum.

TABLE I.
Non-pregnant.

| Gyn. Path. No. | Endometrium | | Ovary | Days after onset of menstruation | Height of tubal epithelium (micra) |
|---|---|---|---|---|---|
| 20186 | Post-menstrual | | — — — | 4 | 21 |
| 16061 | | early | — — — | 7 | 23 |
| 15758 | | early | — — — | 10 | 26 |
| 22919 | | early | — — — | 11 | 29 |
| 22917 | | mid | — — — | 10 | 31 |
| 16651 | Interval ..... | mid | — — — | 13 | 34 |
| 14558 | | mid | — — — | 15 | 26 |
| 23473 | | late | — — — | 14 | 22 |
| 13678 | | late | — — — | 17 | 25 |
| 23030 | | late | — — — | 27 | 22 |
| 2763C* | | early | Corpus luteum | 14* | 20 |
| 21873 | | early | Corpus luteum | 18 | 16 |
| 7952 | | early | — — — | 18 | 18 |
| 27250 | | | — — — | 20 | 20 |
| | Pre-menstrual | | | | |
| 23609 | | | — — — | 24 | 18 |
| 22509 | | | — — — | 24 | 20 |
| 22130 | | | — — — | 26 | 16 |
| 22836 | | | — — — | 29 | 20 |

* Carnegie Embryol. Lab. collection. History of 21 day cycles.

In addition, observations on the state of the surface epithelium of the endometrium were possible in 17 specimens, which were selected according to the criteria described above, and in which the complete endometrium was preserved, extending from the muscular wall to the surface and showing no marked distortion. In seven of these specimens (Gyn. Nos. 22981, 21233, 14236, 22980, 12305, 23412, and 27250) there were no satisfactory sections of the tubes available, while in the remaining 10 specimens (Gyn. Nos. 16061, 22917, 13678, 23030, 7952, 22509, 22919, 22130, 22836, and Carnegie No. 2763) the tubes also were examined, as recorded in Table I. Eight specimens show changes of the premenstrual type and nine resemble the interval phase. The endometrium was classified according to the histological criteria of the phases of the menstrual cycle described by Hitschmann and Adler.

TABLE II.
Pregnant.

| Obs. Path. No. | Duration of pregnancy | Height of tubal epithelium (micra) |
|---|---|---|
| 565 | Early cornual pregnancy | Not above 17 |
| Gyn. 14934 | 6 weeks | Not above 17 |
| 1720 | 8 weeks | Not above 17 |
| Gyn. 18041 | 3 months | Not above 17 |
| 1541 | 3 to 4 months | Not above 17 |
| 837 | Term | Not above 17 |
| 1121 | Term | Not above 17 |
| 1122 | Term | Not above 17 |
| 1388 | Term | Not above 17 |
| 1581 | Term | Not above 17 |
| 1637 | Term | Not above 17 |
| 1716 | Term | Not above 17 |
| 1765 | Term | Not above 17 |

The histological preparations were chiefly the sections used in the gynecological and obstetrical laboratories in the routine case studies. The material was fixed in formalin, cut in celloidin, and stained with hematoxylin and eosin. There were sections from the ampulla or isthmus of the tubes in the 75 specimens of the series. Measurements of the epithelium were made with a Zeiss micrometer from tracings obtained with a camera lucida and oil immersion lens. A Spencer ocular micrometer was also useful.

## OBSERVATIONS

The Fallopian tubes are lined with a single-layered epithelium, consisting of ciliated and non-ciliated cells, as distinguished by Frommel (1886). These cells are distributed about equally and are supported on a connective-tissue stroma. Smaller, rounded cells, with deeply staining nuclei and scant cytoplasm, are scattered here and there in the epithelium, usually close to the basement membrane.

In order to determine the presence or absence of significant variations in structure in the Fallopian tubes during the menstrual cycle and in pregnancy, the entire series of tubes may be considered first. In examining them it becomes evident that the epithelium in certain specimens differs markedly from that in others. At one extreme (Fig. 1) a high epithelium is found, averaging more than 30 micra in height, as measured from the basement membrane to the level of the basal granules of the ciliated cells; the opposite extreme (Fig. 3; Fig. 7) is a low epithelium, averaging not more than 20 micra, measured as above. This marked variation in the height of the epithelium is made more conspicuous by the coin-

cident changes in the morphology of the non-ciliated cells, especially the surface along the lumen, so that when the epithelium is low (Fig. 3; Fig. 7), long, cytoplasmic processes are seen jutting out from the non-ciliated cells as far as the tips of the cilia or even beyond. The nuclei often project into these processes, which may be pedunculated. On the other hand, however, when the epithelium is high, the surface appears fairly smooth, the surface of the non-ciliated cells being at about the level of the basal granules of the ciliated cells. The appearance of an outer row of nuclei is also striking in the high epithelium (Fig. 1), as the nuclei of the ciliated cells tend to lie near the surface. These nuclei are round or somewhat elliptical, rather than elongated as in the non-ciliated cells. This elongation of the nuclei of the non-ciliated cells is especially marked when the epithelium is low.

In the majority of the tubes, however, the epithelium appears to be intermediate in structure, somewhere between the two extremes, as though transitional (Fig. 5). Its surface is less strikingly altered and the cytoplasmic processes of the non-ciliated cells tend to project less than the length of the cilia and are not markedly pedunculated. In general, it is found that the roughened textural condition of the epithelial surface and the length of the processes jutting out from the non-ciliated cells vary inversely with the height of the epithelium. The processes extend farther toward the lumen of the tube, according as the epithelium is found to be lower, and *vice versa*.

Ciliated cells are seen in all of the specimens, without apparent change in distribution.

Having noted the striking variations in structure in this series of 75 tubes, it remains to learn whether these changes maintain a constant relation to the regularly recurring events of the menstrual cycle. It is essential, therefore, to determine whether the two extreme variations in structure of the tubal epithelium actually are found always to be associated with correspondingly contrasting phases in the menstrual cycle, and to correlate the changes in the tubes with coincident occurrences in other parts of the reproductive tract, such as the uterus and ovaries.

When such histological comparison is carried out, it is found that there is a definite relation between the changes in structure in the uterine mucosa and the alterations in the tubes during the menstrual cycle and in pregnancy. Thus, in the 13 tubes obtained during pregnancy, the epithelium is consistently low, averaging less than 20 micra in height, and its surface is strikingly altered by finger-like cytoplasmic projections from the non-ciliated cells. Similarly, in eight specimens from the non-pregnant, in which the endometrium shows the changes (such as dilatation and increased tortuosity of the glands) which characterize the premenstrual phase, as described by Hitschmann and Adler, there is in the tubes a low epithelium, averaging not more than 20 micra in height, and long processes projecting from the non-ciliated cells

In definite contrast to this consistently low epithelium in the tubes from cases of pregnancy, as well as from non-pregnant women during the premenstrual stage, it is found that in tubes from nine cases in which the uterine mucosa shows the characteristic alterations of the interval phase, the epithelium is definitely higher and shows corresponding changes in the morphology of the non-ciliated cells. In this group are found the tubes in which the epithelium reaches the maximal height, associated with the appearance of a definite outer row of nuclei and a flattening of the non-ciliated cells to about the level of the basal granules of the ciliated cells. In some instances the uteri showed borderline changes, such as in transition from the interval to the premenstrual phase, or *vice versa*, thereby suggesting either the post-menstrual or early interval phase. In this group the epithelium of the tubes is likewise intermediate in height and shows other corresponding morphological changes.

Another interesting relation between the changes in the tubes and those in the uterine mucosa became evident in the course of examination of the endometrium. In view of the periodic variations in the structure of the surface epithelium of the uterus in other species, especially in the pig and in the primate *Macacus rhesus*, as Corner (1921 and 1923) has pointed out, the present opportunity was taken to observe the human uterus at various phases in the cycle. In examining the 17 specimens with complete endometrium, a definite change in the structure of the surface epithelium was found, being especially marked by an increase in height of the surface epithelium by the time early premenstrual changes become clearly evident (Fig. 4), as contrasted with the lower height in specimens from the early and mid-interval (Fig. 6, Fig. 2).

With regard to the relation of the changes in the ovaries to the structural state of the tubal epithelium during the cycle, it was found that in the two specimens available, a section of the ovary showed a recent corpus luteum (Fig. 8) with well developed lutein cells, probably at or near maturity, while in the tubes (Fig. 3) there was a low epithelium with long cytoplasmic processes. The endometrium (Fig. 4) in both cases showed the changes characteristic of the early premenstrual phase. Similarly, a low epithelium is consistently seen during pregnancy (Fig. 7), when the corpus luteum is known to be large and well differentiated.

## Discussion

In the present study, based on observations on 75 specimens of Fallopian tubes which are not obviously pathological and in which a detailed history indicates no marked abnormalities of the menstrual cycles, there is found a single-layered epithelium composed of ciliated and non-ciliated cells and smaller, rounded cells, scattered usually near the basement membrane. This lining

epithelium shows marked differences in structure in different specimens, involving the height of the epithelium and the morphology of the non-ciliated cells. A striking consistency is apparent in the relation of these structural variations: when the epithelium is at its maximal height, its surface is fairly smooth, the non-ciliated cells being flattened to about the level of the basal granules of the ciliated cells, and the appearance of an outer row of nuclei is definite (Fig. 1). When the epithelium is about the minimal height, its surface is roughened, owing to the presence of cytoplasmic processes which jut out from the non-ciliated cells to the tips of the cilia or even farther (Fig. 3; Fig. 7).

Correlation of the structural modifications of the tubal epithelium with various phases of the menstrual cycle is based chiefly upon comparison of the coincident morphological changes in the uterine mucosa. This comparison was made with 18 specimens from the non-pregnant at various phases of the cycle and 13 specimens from the pregnant. In tubes obtained during pregnancy, and in specimens with non-pregnant uteri showing the histological characteristics of the premenstrual phase, it is found that the tubal epithelium is consistently in that stage which is marked by a minimal height and long cytoplasmic processes of the non-ciliated cells. Epithelium of a maximal height, with fairly smooth surface and a definite outer row of nuclei, is found uniformly in specimens with uterine mucosa of the interval phase. When the endometrium shows transitional changes from the interval to the premenstrual phase, or *vice versa*, the epithelium of the tubes appears correspondingly intermediate between its two extreme variations in structure. Corpora lutea, at or near maturity, are associated with low tubal epithelium, corresponding to the early premenstrual phase in the endometrium of the two specimens at hand.

Correlation of the changes in the tubal epithelium with the date of menstruation, as given in the history, is especially interesting in an attempt to get a working hypothesis as to the time of ovulation in the human reproductive cycle. In the pig it has been found that the period when the ova are passing through the tubes is marked by characteristic structural changes in the tubal epithelium, especially the attainment of the maximal height and smooth surface. This would suggest that in the human, at the time when the tubal epithelium reaches its maximal height and presents a histological picture almost identical with that of the pig, there may be associated a similar functional activity, namely, ovulation. According to this method, it is evident that in 12 specimens of the present series the tubal epithelium is at a maximal height, averaging at least 30 micra, and shows the histological changes which are seen in the tubal epithelium of the pig only about the time when the ova are in transit through the tubes. If the menstrual histories in these cases are considered, it is found that the time in the cycle when the tubes were removed averages about 13 days after the onset of menstruation.

This striking alteration in the tubal epithelium may also be correlated in the menstrual cycle by determining the phase in the uterine mucosa with which it is coincident. Thus, as summarized in Table I, it seems evident that the endometrium shows the changes of about the mid-interval stage, when the structural alterations of the tubal epithelium are very similar to those found in the pig's tube about the time the ova are in transit.

Furthermore, the relation between menstruation in man and oestrus in the pig is evident from a comparison of the tubal epithelium in the two species. In the human, the morphological alterations in the tubal epithelium during pregnancy, or when the endometrium shows premenstrual changes, are closely parallel to the histological changes in the tubes of the pig during the implantation phase, or in pregnancy. Thus, in the human, menstruation is associated with structural changes in the epithelium of the tubes, similar, to a considerable degree, to those which mark the implantation phase in the pig. Oestrus ("heat"), on the other hand, has been shown by Corner to accompany ovulation in the pig. It seems evident, therefore, that the striking external manifestations of the mammalian reproductive cycle which are associated with oestrus in the pig and with menstruation in the human mark contrasting phases in the cycle.

The functional significance of the curiously altered surface of the tubal epithelium during the premenstrual phase and in pregnancy, when the long, cytoplasmic processes of the non-ciliated cells jut out, is not clear, though apparently similar structural alterations in the surface epithelium of the uterus in the pig facilitate implantation of the embryos, as Corner has demonstrated. It is suggested that possibly the coincident appearance of similar structures in the tubal epithelium may indicate a response common to these derivatives of Müllerian tissue. Similarly, in the surface epithelium of the uterus in the human, Geist (1913) has described "Propfzellen" or "Knopfzellen."

Cilia are found throughout the menstrual cycle and pregnancy without apparent variation in number. This observation, and similar observations on the pig's tube (Snyder, 1923), seem to cast great doubt upon various clinical hypotheses which attempt to explain pathological conditions, such as tubal pregnancy, placenta praevia, and sterility, by supposed cyclic variations in the number and activity of the tubal cilia.

In brief, anatomical consideration of the Fallopian tubes indicates that in the course of the menstrual cycle two chief phases in the structure of the tubal epithelium stand out in contrast to the less conspicuous transitional states: one (low epithelium) coincident with the premenstrual phase in the uterine mucosa or occurring in

pregnancy, when the corpus luteum is known to be well differentiated; the other (high epithelium) attaining a maximum about the mid-interval phase in the endometrium. Comparison with the pig suggests that the former (low epithelium) marks the period between ovulations, the latter (high epithelium) the functional phase, during which the ovum passes through the tube.


### Summary

1. There are periodic changes in the human Fallopian tubes which involve the height of the epithelium and the morphology of the non-ciliated cells.

2. The cyclic changes in the tubes are closely parallel chronologically to the alterations in the endometrium during the menstrual cycle.

3. Pregnancy inhibits the cyclic alterations in the tubes and the epithelium remains in the condition which is found in the premenstrual phase.

4. Cilia are seen throughout the cycle without apparent change in number.

5. These observations give no support to hypotheses which explain sterility and pathological conditions of implantation upon the basis of alternations in ciliated and non-ciliated (secretory) phases in the epithelium of the tubes.

6. Comparison with the pig suggests;

(a) That the changes in the human tubes during the premenstrual phase are closely parallel to the alterations which are found in the tubes of the sow during the implantation period.

(b) That similarly, about the mid-interval in the human, there are changes in the tubal epithelium which closely resemble the histological alterations in the tubes of the pig during the ovulation period.

(c) That inference on this basis would indicate the probable time of ovulation in this series to be about 13 days after the onset of menstruation.

(d) That menstruation in the human and oestrus ("heat") in the pig are marked by changes in the tubal epithelium which are in striking contrast and are found at different phases of the cycle.

7. There are periodic changes in the surface epithelium of the uterus during the menstrual cycle.


I am indebted to Dr. G. W. Corner for generous suggestions and criticism throughout the present undertaking.

### DESCRIPTION OF PLATE

Fig. 1.—Human oviduct about mid-interval stage. Camera lucida drawing, ×700.

Fig. 2.—Endometrium about mid-interval stage, obtained from same specimen as tube shown in Fig. 1. Photograph, ×95.

Fig. 3.—Tube at premenstrual stage. Camera lucida drawing, ×700.

Fig. 4.—Early premenstrual endometrium, obtained from same specimen as tube shown in Fig. 3. Photograph, ×95.

Fig. 5.—Tube about late interval stage, as indicated by the coincident state of the endometrium. Camera lucida drawing, ×700.

Fig. 6.—Early interval endometrium showing state of surface epithelium. Photograph, ×95.

Fig. 7.—Tube from pregnancy at term. Camera lucida drawing, ×700.

Fig. 8.—Corpus luteum obtained from same specimen as tube shown in Fig. 3 and endometrium shown in Fig. 4. Photograph, ×7.

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Tube

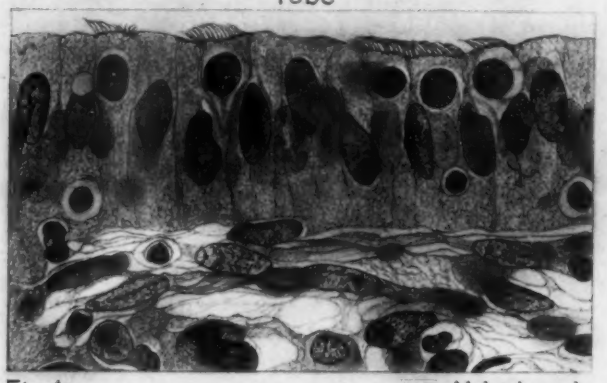

Fig. 1 Mid-interval

Fig. 3 Premenstrual

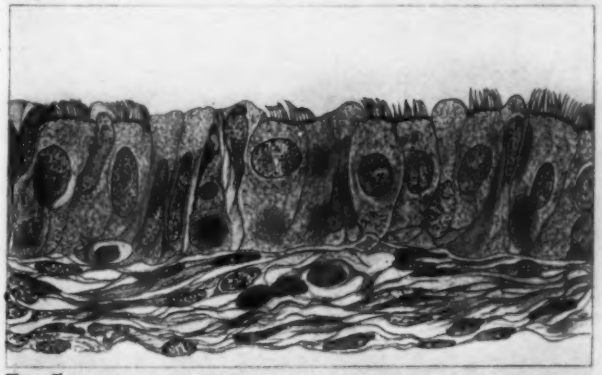

Fig. 5 Late interval

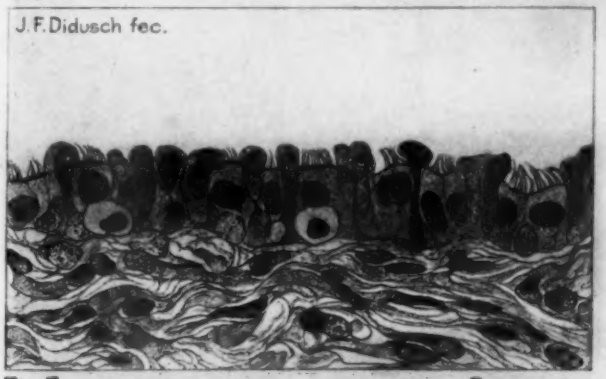


Fig. 7 Pregnancy

Uterus

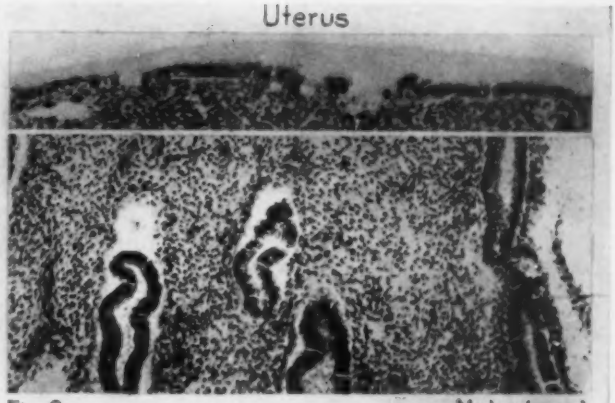

Fig. 2 Mid-interval

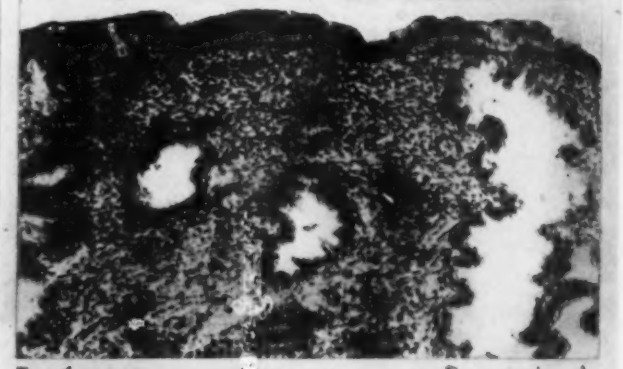

Fig. 4 Premenstrual

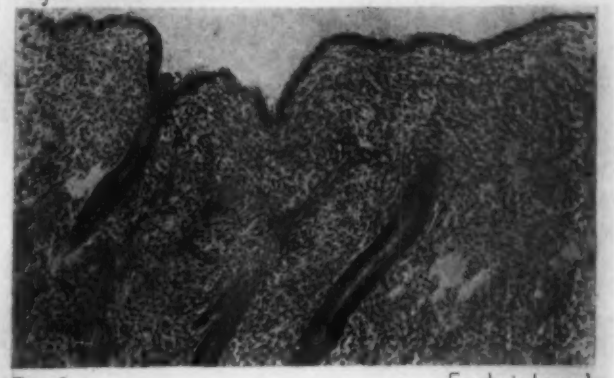

Fig. 6 Early interval

Fig. 8 Corpus luteum

# THE ACUTE EXANTHEM OF LEPROSY

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Leprosy, thanks to intensive sanitation, has almost disappeared from Europe. Unfortunately, the same cannot be said of the countries of Latin America in all of which cases of this terrible disease occur in varying numbers. In Colombia there are three Leper Colonies, Agua de Dios, Contratación and Caño de Loro which house approximately 6500 lepers, and afford an opportunity for studying the phenomena which occur during the course of the disease, and for the study of the pathology, prophylaxis and treatment. Among the patients who are under observation from day to day it is possible to observe manifestations of leprosy which are rarely seen even by physicians who live in places where leprosy is common but whose practice is carried on outside leper hospitals.

Among the patients in these leprosaria it is not uncommon to see acute phases of leprosy which occur at more or less frequent intervals during the chronic course of the disease, or which are the first clinical manifestation of infection in apparently hitherto healthy individuals. These acute attacks are preceded by a definite, though short, prodromal stage which is followed by a febrile attack and the appearance of a nodular eruption on the body associated with certain visceral symptoms. Such an attack is quite ephemeral and its entire course may pass unnoticed except in hospitals where the physician has the opportunity to see the patients daily. These acute manifestations which occur as exacerbations during the course of chronic leprosy, constitute in reality an *acute exanthem*, by which term, or by the word *exacerbation*, we shall refer to them in this paper.*

In recent years a number of authors have mentioned the possibility of the occurrence of acute exacerbations during the course of leprosy, but they have never clearly described them in their publications. Other authors, by whom the description has been attempted, have confused the manifestations of the acute exanthem with other signs of the disease, probably because the small number of observations which they were able to make did not permit them to differentiate the acute exanthem clearly from changes which occur as a result of the chronic infection. The symptom complex of which the acute exanthem consists was called "leprosy fever" by McDonald,[1] who observed 21 cases which occurred during two years among the 235 patients under his care, that is to say, in less than nine per cent of the total number of lepers. He emphasized as an important fact that none of the patients had had these attacks before their entrance into the lazaretto. Dyer,[2] in his description of the evolution of the disease, spoke of the temperature curve in the 'fever of leprosy' as a 'definite entity.' Perrin[3] and MacLeod,[4] in their descriptions of the chronic course of tubercular leprosy, included symptoms which were in our opinion those of the acute exanthem. Rivas and Cossio[5] would seem to agree that leprosy is an infection which progresses by stages and which shows periods of improvement, during which the patient apparently may be even cured, interspersed from time to time by relapses.

In view of the above discrepancies, we hoped to establish definitely the differences between the characteristics of chronic leprosy and the syndrome of acute symptoms which occurs at successive intervals and constitutes what we shall call *the acute exanthem of leprosy*. We hoped to show that during the period of acute symptoms the condition not only of the patient but also of the lepra bacillus undergoes a change from that in which it exists during the periods of chronicity, and we hoped that we could demonstrate satisfactorily that marked differences exist between the chronic lesions of the disease and the nodular eruption which develops in the acute stage. In the Leper Colonies in Colombia the patients themselves speak of the acute attacks as 'attacks of nervous fever,' a name which summarized the principal symptoms, the fever, and the painful sensations from which they suffer with each crisis.

*Predisposing Causes.*—The acute exanthem of leprosy occurs in both sexes, and in patients at any period of life from childhood to old age. The attacks occur, however, with greatest frequency in adult life, and in patients of a plethoric constitution. Race has no influence on the liability to exacerbations. White patients are attacked

* These acute attacks were given the name "Brotes agudos" in the original copy of this paper which was written in Spanish. The word *brote* in Spanish signifies a skin lesion, (a breaking out), and it has seemed to translate the word *exanthem*, since the attacks are characterized by an acute cutaneous eruption and a general reaction with an ephemeral fever. The word *exacerbation* is applicable to the majority of these attacks, since they occur acutely during the chronic course of the disease. To some of them, however, the word *exacerbation* cannot be applied, since they form the apparent initial clinical manifestation of the disease.

as often as Negroes or the more or less mixed Indians. The occupation and circumstances of the leper have no influence, and the exanthem occurs alike in rich and poor. It is seen in the tubercular, mixed and maculo-anesthetic forms of leprosy.

Physiological changes in the host afford a propitious occasion for the beginning of an exacerbation. Parturition or the beginning of menstruation may be followed by the initial attack. This happened in the case of a young girl in whom leprosy had been diagnosed previously only from the presence of sensory changes—for example, she had frequently been burned without feeling pain. On the establishment of menstruation an acute eruption of large red maculae appeared on her arms and knees and remained permanently.

It is not uncommon to see severe exacerbations following marriage among lepers. For example, in two young patients who had had benign erythematous spots, acute exanthems of the severest sort and of long duration, which greatly increased the severity of their disease, appeared in the days immediately following their marriage.

The immoderate use of alcohol is a common reason for the occurrence of repeated attacks. An excess of physical work is another exciting cause. Many patients come to the physicians in our lazaretto with the first symptoms of an exacerbation after a single day of work in the fields, in the open air at a tropical temperature of 35° C., to which they have not been accustomed.

Anything which tends to depress the mind of a leper disposes to the acute exanthem.

We have become convinced that treatment, even those forms which have acquired the reputation of being most effective against leprosy, may bring on the attack. The administration of potassium iodide is frequently followed by the appearance of the acute exanthem. Chaulmoogra oil or sodium gynocardate or the ethyl esters of gynocardic acid may all act in this way and the first treatment which the patient receives may precipitate an acute exacerbation. The patients, therefore, themselves desire to stop the medication as soon as they feel the first symptoms of the exanthem, or to postpone further treatment until the acute manifestations have disappeared.

The above conditions are those which initiate many of the exacerbations, but sometimes they occur without any apparent cause.

It is well to mention that when leprosy is associated in the same patient with other infectious diseases developing at the same time—tuberculosis, paludism, dysentery and so on—while these run their ordinary course, the leprosy continues as though uncomplicated by the other maladies, and Hansen's bacilli carry on independently their function of slow destruction.

### Description

In order to render our description of the exanthem as clear as possible we shall discuss a typical attack as it occurs in a case of nodular leprosy showing all the stigmata of the disease—maculae, alopecia, changes in cutaneous sensibility, infiltration of the tissues, etc. During the chronic stage of this condition which permits the patient to carry on his daily occupations and leaves him in a state of comparative comfort, his equilibrium is suddenly disturbed by the prodromal symptoms of the exanthem. These prodromata consist of vague pains, not only felt on the surface of the body, but also referred to the deep muscular tissues. There are also mild pains in the joints, and mild chills or chilly sensations which precede an abrupt rise of temperature of medium height. These symptoms precede the appearance of cutaneous manifestations of the exanthem by 36 or 48 hours.

The malaise which the patient experiences is not sufficient to send him to bed, but does not permit him to do any active work. Cephalalgia and loss of appetite, conditions which are so frequent among the prodromata of other infectious states, are uncommon in this exanthem.

The character of the pain in the limbs differs from the pain of leprous neuralgia, in that it does not follow the course of the nerves, nor does it have the paroxysmal and severe character of the neuralgic pain. It is a vague, constant pain which does not settle in the joints as does that of rheumatism; nor does it impede motion. Pressure over the muscles increases the pain. Tenderness may be so marked and certain spots may be so sensitive that even contact with the bed annoys the patient.

The chills may come on at any time of the day. They are not severe, and are not single, and intense, like those of malaria or some other infectious diseases. Sometimes they do not amount to more than chilly sensations.

Almost immediately visceral disturbances occur, but digestive symptoms are rare. Vomiting is present only in those patients who have been subject previously to gastrointestinal upsets. Diarrhœa is uncommon; if it occurs, it appears late in the course of the exacerbation. More frequent is the occurrence of marked intestinal constipation. The liver is slightly enlarged. Its border may descend 2 or 3 cm. below the costal margin and be tender on palpation.

Sometimes the exanthem may begin with signs of pulmonary congestion. In one case, that of a young woman, there were signs of pulmonary congestion over the entire right lung. At the end of three days the congestion diminished and simultaneously with its disappearance the exanthem came on. One woman, who during the pulmonary trouble had been confined to bed, got up and in spite of the fever walked about.

At this stage of the attack a brawny edema of the face, forearms, hands and of the legs and feet occurs. As a general rule, this symptom disappears after the complete development of the exanthem. The edema depends in part upon the obstruction of the finest blood vessels in the affected areas and in part on an acute leprotic ne-

phritis. This nephritis is due to the continual expulsion of lepra bacilli through the kidney in the urine, where they may be found on bacteriological examination with the albumin which results from their passage.

In some patients the spleen is enlarged perceptibly, but it must be remembered that the Colombian leper colonies are in the tropics and consequently the patients may be victims of chronic malaria. The heart, which may be slightly dilated, may have murmurs at the base, and recover its normal condition only by degrees.

However, patients with chronic mitral insufficiency may suffer at the beginning of the acute attack from a complete decompensation with hepatic and renal congestion. One of our patients succumbed in this way in the course of an acute exacerbation.

The fever during the acute attack is of great interest. We have taken the morning and afternoon temperature of many patients from the beginning to the end of the attack. The following charts have been selected as typical. They show that the single character common to all cases is the termination of the fever by lysis.

CHART I.

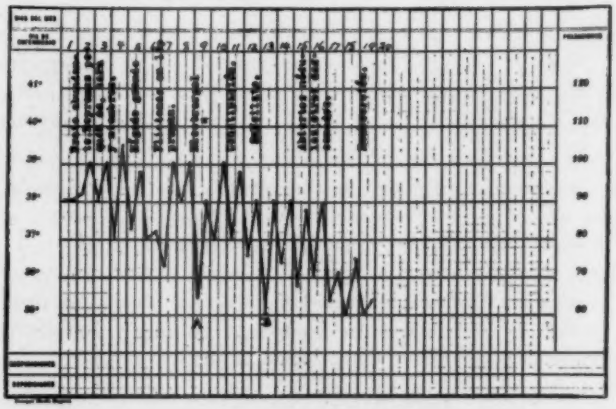


CHART II.

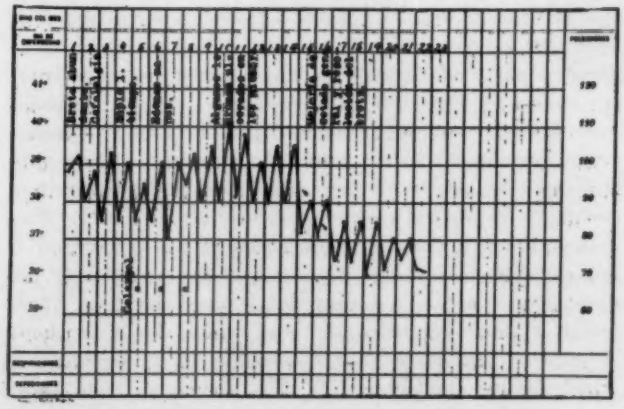


CHART III.

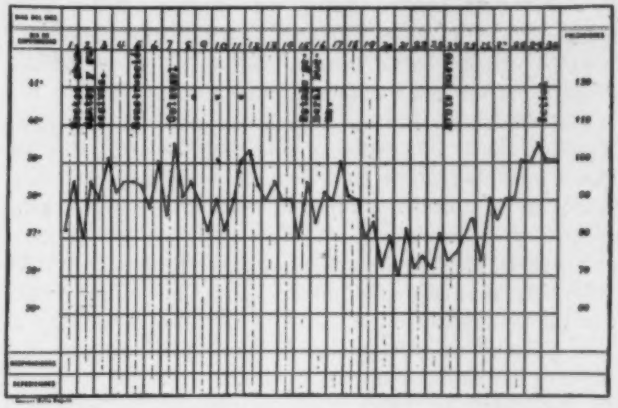
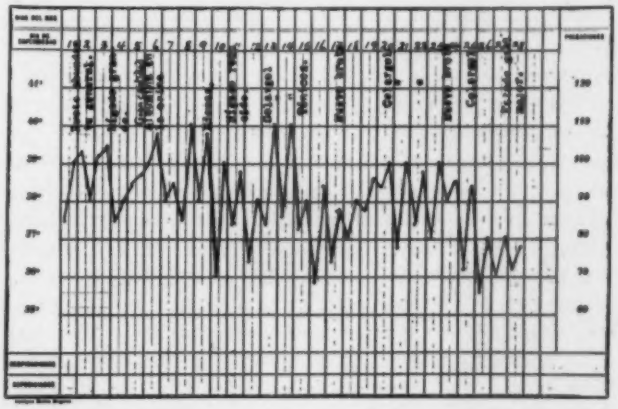


CHART IV.



The fever reaches its maximum in a variable length of time, usually between the first and the third day. The highest temperature in the series which we studied was 40.3° C., but in most cases it varies between 38.5° and 40° C. The maximal temperature is maintained for from 24 to 72 hours; after which the temperature curve begins to descend and the fever terminates by a *characteristic lysis*. The daily descent is gradual and the temperature falls in the majority of cases 0.5° C. daily. It is not unusual to find patients in whom the daily drop in temperature during its descent amounts to 1° C. a day. Although in most of the cases the temperature becomes normal in six days, the fever may last 12 and under exceptional conditions 20 days. There is no appreciable difference in the temperature charts of patients of different ages and different races.

After the prodromal period and the beginning of the fever at the end of the second to the fourth day during the ascent of the temperature, the typical cutaneous changes appear. The full development of the eruption occurs during the period of lysis. Consequently, a curve representing the severity of the cutaneous eruption would

attain its maximum during the descent of the temperature curve; in other words, the two lines would cross on a chart. In this way leprosy resembles many other infectious diseases which attack the skin. Some of the eruptive fevers may behave in the same way.

The cutaneous manifestations of the acute exanthem of leprosy consist of erythema, and nodules which are at their beginning perceptible only to the sense of touch. Small areas of erythema of a dull deep rose color may be seen on the skin surface of whites, mulattoes or Indians. In negroes the erythematous areas are slate gray in color. These areas correspond to subjacent nodules which are the primordial elements of the cutaneous manifestation of the acute exanthem of leprosy. The patients complain of a burning sensation in the skin, sharply localized to these nodules, which they compare to the sensation which would result from sprinkling the skin with very hot oil.

The nodules are rounded, smooth, and at first can be perceived only by the touch (Figs. 1, 2). They are adherent below to the subcutaneous tissue and are attached to the cutis vera at their borders. The apex of the nodule is not adherent to the skin, which is freely movable over it. If the skin over it be incised, the surface of the nodule is readily freed from the surrounding tissues along definite planes of separation; the base, however, adheres closely to the underlying parts. Some of the patients slit the skin above the nodules, and by energetic squeezing extract their contents without haemorrhage. They claim to experience a considerable relief from this procedure. The dimensions of these nodules vary from the size of a grain of millet, 1 to 2 mm. in diameter, to a diameter of 3 cm. Their consistence is about that of rubber, but they are not quite so elastic.

The anatomical origin of the nodules is in the cellular subcutaneous tissue. While they occupy this layer alone, they cannot be seen. Soon, however, they grow until the surface of the nodule is tangential to the surface of the skin. They then form an arc which may become a hemisphere above the level of the epidermis. The form of the nodule is modified by the amount of subcutaneous connective tissue. For example, on the forehead and the chin they are slightly flattened, since in these regions they are compressed between the skin and the bony framework of the face. In the lobule of the ear where the nodules are smaller than in any other part of the body, they appear as tiny spherules, which can be felt between the fingers and which are translucent when the lobule is under tension.

Some authors have stated that sensibility in the nodules, as in the other manifestations of leprosy, is diminished. We believe that the sensibility of these nodules depends not so much on the nodules themselves as on the integrity of the nerve fibres supplying the region in which they are situated. Some nodules are very tender; in others anesthesia is complete, or sensation is diminished according to the abundance or lack of the sensory function of the nerve supply of the region.

The nodules are formed in different areas of the skin of the body successively, so that it would be possible to make a diagram showing the order of their occurrence. Generally, they appear first on the face, on the malar region and on the cheeks. Simultaneously or immediately afterward they may be found on the upper extremities, on the anterior and posterior surfaces of the forearms, the elbows and the upper arms, the internal surfaces of the latter being generally unaffected. In the lower extremities they are found first on the anterior surfaces of the thighs. There may be, however, exceptions to this rule. For example, one young woman, who was observed during several exacerbations, had during the first attack nodules only on her lower extremities. In her second, which was more severe, the nodules were present also on the upper extremities, but in neither attack was her face implicated. Any region on the body may be infiltrated with these nodules, but the back of the neck and the nose are only occasionally affected. On the palms of the hands and soles of the feet a few nodules may develop which are always very painful because of the thickness and inelasticity of the skin in those regions.

In severe attacks the mucous membranes of the larynx, uvula, soft palate, tongue, vulva, vagina, are also implicated. Sometimes hard, red, flattened nodules may be found on the glans penis.

In some attacks the nodules may be few and discrete. In severe cases, however, when they are far advanced or when a new crop of nodules succeeds the first at the end of its development, nodules may form between those of the first lot, so that they tend to coalesce and form lepromata which may be from 4 to 10 cm. in diameter, reddened and raised, with a smooth surface (Fig. 3).

The fate of the nodules is variable: some undergo complete resolution. This is common among robust patients after a first attack. In other cases, after from 4 to 8 days the rose color of the nodules changes to a dark red; the nodule becomes slightly softened and disappears little by little, leaving behind a pigmented area of a purplish color over which there is a furfuraceous desquamation which is visible because of its contrast with the smooth surface of the surrounding skin (Fig. 4). Sometimes the nodules break down and ulcerate. When this happens from one to six days after their appearance, they develop a yellowish vesicle in the center (Fig. 3). The material which they contain becomes thickened and a flat crust is formed over the apex of the nodule. If the vesicles are broken, a superficial ulcer develops, from which a thick lymph exudes and which heals without treatment, leaving behind a whitish, irregular cicatrix which is not characteristic. The discharge from these

ulcers contains small numbers of lepra bacilli occurring singly or in clumps.

We believe Perrin[5] to be in error when he says that these ulcers may go on to destroy muscles, tendons and bones and cause mutilating leprosy. We have never seen such a result follow these ulcers. Mutilating leprosy results from gangrene of the skin which is a very different condition and is known to the patients in our leper colonies by the expressive name of "vejigon blanco" or "vejigon negro" according to the appearance of the destructive lesion.*

Erysipelas which very commonly complicates leprosy may sometimes develop in the same area of the skin which contains these nodules.

*Varieties of the acute exanthem.*—There is a transitional form of macular leprosy which in the majority of cases becomes the nervous type, but in certain instances changes later into the tubercular form. In these patients, the same exanthem occurs, with the same fever and with similar prodromal symptoms—the same syndrome, except that, instead of nodules, circumscribed red blotches (maculae) with circular borders develop. Eventually these fade in the center, and finally become converted into bronzed spots which are known clinically as 'manchas pigmentadas'—pigmented spots. In the macular form of leprosy, however, the acute exanthem may be followed by a change to the tubercular type.

In the nervous type of leprosy sharp exacerbations may occur which correspond to the attacks of exanthem just described. These are characterized by slight afternoon temperature and very severe neuralgic pains, which drive the patient almost to desperation and are very difficult to alleviate by ordinary therapeutic agents. At the end of a few days (15-30) muscular atrophy develops rapidly, if it has not already existed. For example, a woman who had been treated by the physicians where she lived for rheumatism because of the mildness of her leprous symptoms, after three years' residence in the lazaretto came down with a neuralgic attack of 20 days' duration, during which she became paralyzed very suddenly because of atrophy of the muscles of her arms and legs. The same sort of fulminating process was seen in a patient who had been previously very robust, but who at the end of one month was forced to take to his bed because of atrophy of the flexor muscles which followed a severe neuralgia of the circumflex and sciatic nerves so that he could take only a few steps with the aid of an attendant.

In this connection we have some findings which are interesting in the light of a recent article of Gougerot.[6] We would call attention to the frequency of mental changes in the form of acute mania—psychic exacerbations—which may in all probability represent the acute exanthem. We have seen one patient, a woman with a very severe infection, who suffered from an acute mania during the course of a typical exacerbation. During this attack she died. The autopsy showed the three meninges adherent in a single mass and an active and passive congestion over the cerebral convolutions, findings which were confirmed in several other cadavers. These anatomical lesions explain the psychic exacerbations which occur during the course of cerebral leprosy and actual cerebral infection is not improbably accountable for the easily aroused cerebral excitation in the leper as an individual and as a group when collected in leper colonies. This irritability of the leper in hospital surroundings has been noted by Castellani and Chalmers.[13]

*Evolution of the exanthem.*—An acute exanthem, which may be mild or severe, may be the first manifestation of a leprosy, which, until its occurrence, has remained latent and unrecognized. It sometimes happens that during the chronic stage there is continual formation of a few nodules in the skin. Their appearance is accompanied by neither fever nor any other general reaction and does not on the whole constitute an acute exanthem.

After the return of the temperature to normal—which patients themselves call graphically, 'marchitarse la fiebre' (the withering of the fever)—the reabsorption of the nodules, and cicatrization of the ulcers when suppuration has occurred, the patient, although somewhat anemic and attenuated, enters on a period of relative calm, and the chronic stage resumes its course.

In some cases, however, the first attack may be followed immediately by a second, and one attack may follow another, so that we have seen patients in the asylum who have undergone one exanthem after another for a period of four years. At the end of such a series they may manifest so great an improvement as to seem practically cured, although their bodies may be covered with the scars of the ulcers. On the other hand, they may be unable to stand so great number of exacerbations and may develop a chronic diarrhoea with extreme emaciation, and die of debility.

*Bacteriology.*—Just as there is great variety in the symptoms of leprosy, there is also considerable difference in the nature of the lepra bacillus; and this is most easily observed during the acute exanthem. In general, Hansen's bacilli may be found singly or in groups in the nasal mucus, in the secretions or discharges from the body, and in the lymphatic fluid expressed from punctures in the skin. Nevertheless, in many cases of tubercular leprosy it is impossible to find them. Whether erythematous or pigmented spots or nodules or ulcers are examined, they are apparently sterile. On the other hand, it may be possible a few days later to obtain beautiful preparations

* The large bulla common in pemphigus is known to the laity in Latin American countries by the name "vejigon," (bleb or bladder). Owing to the resemblance between the lesions that appear in gangrene of the skin and the bullae of pemphigus, the same word is used by the lepers for both conditions.

of characteristic bacilli with the same technique, from the same areas. Hence it may be seen that the diagnosis of leprosy has to be made mainly on clinical grounds. In acute exacerbations of the malady analogous conditions may prevail. Alongside nodules which contain bacilli, others may exist in which they cannot be found. The vesicles and pustules which may be formed during the acute attack never contain pyogenic microorganisms, but in the majority of cases lepra bacilli may be found in them. The contents of others, however, may be absolutely sterile.

During the acute exanthem Hansen's bacillus may undergo certain changes in morphology and staining characteristics. Sometimes the bacillus is very resistent to acid alcohol and stains very intensely with fuchsin; then, again, it may be stained a pale rose color, probably because the protective capsule which is responsible for the staining reactions of the organism is not normal. This represents a change of structure corresponding with a change in function. The protoplasm of the bacillus frequently shows a process of disintegration and fragmentation into granules so that the organism may resemble a chain of beads. This change is also found in cases of leprosy of long standing or under certain other conditions, for example, after treatment with chaulmoogra oil or its derivatives. This would seem to indicate that these changes are the result of injury to the bacillus. When these granular bacilli disintegrate completely, there remain the granular masses which McDonald has called "bacillar detritus." It is generally recognized that granular disintegration is a phenomenon which in many bacilli accompanies the loss of vitality and the death of the organism; and no doubt the granular disintegration of bacilli during an acute exanthem is susceptible of the same interpretation.

*Humoral reactions.*—We have made studies of the blood by histological and bacteriological methods and we have made bacteriological studies of the urine. We carried out these studies on four patients with chronic leprosy and on six with the acute exanthem.

*Urine.*—We found no appreciable changes in the phosphoric acid and urea excretion either in acute or in chronic cases from that of normal people living in the same localities. The urine of chronic cases of leprosy contains albumin. The chronic nephritis of leprosy, which is probably a toxic manifestation of the disease, is almost universal in leper colonies and with pulmonary tuberculosis is the most common cause of death of the patients. In acute attacks the amount of albumin is increased almost constantly (Chart V).

Urobilin was found in two of the four chronic cases and in the urines of all the acute cases examined. That there is a disturbance in liver function in lepers is indicated also by anatomical changes found at autopsy. The liver of the leper is usually large and yellowish. The surface is smooth and shows signs of cirrhosis caused by lepra bacilli which are to be found in the tissue.

The sediment in the centrifuged urine from both acute and chronic leprosy contains lepra bacilli, but they are much more numerous in acute cases. These bacilli can be recognized from all other acid-fast organisms in the urine by their peculiar grouping.

*Blood.*—The percentage of haemoglobin is high in lepers. Anemia, when it occurs, is very mild. Haemoglobin is conserved in chronic cases of leprosy and the amount is decreased only in very advanced cases or when some other disease (generally tuberculosis) is associated with it. Tuberculosis, as we have said above, is the cause of death in the majority of lepers not only in the leper colonies in Colombia but also in those of other countries. In one of our patients who suffered from repeated acute attacks the haemoglobin fell only 5% below normal.

The blood clots very rapidly, so rapidly indeed as to interfere sometimes with intravenous medication. The clotting time in chronic patients is from 6 to 7 minutes; in patients with the acute exanthem it is only 5 or 6 minutes. This fact is appreciable without the aid of special instruments. When small incisions are made to remove lepromata for examination, the blood clots as soon as it escapes from the vessels.

As a general rule, the leucocytes are increased in all forms of leprosy, but the white count is even higher during the acute exanthem. We were surprised to find that during the first attack one of our patients had a white count of 30,000 (Chart VI).

CHART V.

| Urine liter | Chronic cases | | | | Acute exanthem cases | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 1 | 2 | 3 | 4 | 5 | 6 |
| Urea | 13.3 | 24.2 | 16 | 20 | 21.7 | 17.6 | 27.1 | 17.6 | 13 | 17 |
| Total phosphoric acid | 1.6 | 1.5 | 0.7 | 1.6 | 2.5 | 0.4 | 0.8 | 0.7 | 1.7 | 1.9 |
| Albumin | — | 0.3 | — | — | 0.7 | trace | 1 | trace | trace | trace |
| Biliary pigments | — | — | — | — | — | — | + | — | — | + |
| Indican | — | + | — | — | — | — | — | — | — | — |
| Acetone | — | — | — | — | — | — | — | — | — | — |
| Lepra bacilli | + | + | — | — | + | — | + | + | — | + |

CHART VI.

| Blood | Chronic cases | | | | Acute exanthem cases | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 1 | 2 | 3 | 4 | 5 | 6 |
| Coagulation time. Minutes | 7 | 6 | 6 | 7 | 5½ | 6 | ? | 6 | 6 | 5 |
| Per cent haemoglobin | 80 | 70 | 80 | 85 | 65 | 80 | 80 | 90 | 90 | 95 |
| W. B. C. | 12000 | 8800 | 12200 | 10500 | 15000 | 13000 | 30000 | 11200 | 10400 | 9200 |
| Differential count: | | | | | | | | | | |
| P. M. N. | 66 | 51 | 40 | 59 | 66 | 62 | 63 | 58 | 63 | 53 |
| E. | 4 | 8 | 31 | 12 | 3 | 10 | 1 | 2 | 1 | 4 |
| B. | 1 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 1 | 1 |
| L. M. | 11 | 16 | 6 | 12 | 9 | 1 | 12 | 6 | 4 | 10 |
| Lymph. | 15 | 21 | 21 | 15 | 12 | 23 | 18 | 31 | 30 | 28 |
| T. | 1 | 3 | 1 | 1 | 4 | 1 | 2 | 2 | 0 | 2 |
| Endothelial cells | 2 | 1 | 0 | 1 | 6 | 3 | 4 | 1 | 1 | 2 |
| Hansen's bacilli in the blood | — | — | — | — | — | — | — | — | — | + |

The differential count in acute and chronic leprosy coincided in our study with the earlier observations of Gougerot, that is to say, there is a relative increase in polymorphonuclears and a decrease in number of eosinophiles. After the crisis, there is a marked tendency toward a relative mononucleosis and eosinophilia. The mononuclears, large and small, were never decreased in number.

Of special interest is the presence of elements in the circulating blood in this disease, whose origin is quite clear. These are endothelial cells with rectilinear borders where they are joined with other cells to form the vascular endothelium. Leprosy is a disease which tends to localize itself along the course of circulatory channels and it is easy to believe that these cells are desquamated from the blood vessels under the influence of the infection. We have seen these cells in small numbers (1 or 2%) during the chronic stage of the disease, but during the acute exanthem their number is increased to from 4 to 6 per cent of the total number of white cells.

In looking for lepra bacilli in the blood we treated it with a 5% solution of acetic acid and examined the sediment for bacilli, which were, however, found in the blood of one patient only, who was suffering from his second exacerbation. We are led to believe that the statements of certain authors that during the febrile crises Hansen's bacillus enters the circulation, and that the disease becomes a bacteriaemia, are in some cases at least correct.

We determined in these cases the Arneth formula concerning which in leprosy we have not seen any recent work. There is a deviation to the left in this formula in the blood in both the acute and chronic stages in leprosy.

### Pathological Histology

In order to compare the histology of the acute nodules with that of the chronic tubercule we have made numerous biopsies. We have studied old chronic tubercles and fresh nodules from the same patient.

When they are dissected from the skin the nodules appear spherical or oval. They are formed along the course of the lymphatic vessels in the cellular subcutaneous tissue. We have in one case dissected out a segment of such a vessel, 12 cm. long, to which were attached five nodules, so that the whole specimen resembled a string of beads. They are usually smooth, but they may be studded with tiny rounded projections (mammillated), and they are cream-colored. On section, they are seen to be surrounded by a dense fibrous layer, but this is not a capsule and is only different from the center of the nodule in that the latter is softer. In microscopic sections it is seen that the overlying epidermis is normal. All the changes have occurred in the dermis and the cellular subcutaneous tissue and are of an inflammatory nature. Newly formed capillary vessels (Fig. 6) are very numerous. There is hypertrophy of the connective tissue beneath the epidermis, and the cutis vera is made up of very dense bundles of fibrous tissue comparatively poor in its content of connective-tissue cells. In the spaces between these bundles of fibers are many mononuclear cells. Embedded in this dense connective tissue are numerous vascular areas sharply outlined from the tissue above them (Fig. 5). These areas are made up of a network of very fine fibrous tissue densely infiltrated with round cells and are very vascular. Many of the vessels in this tissue are lined with endothelium, which is very much swollen, and in some of these vessels the cells of the endothelium have proliferated to such an extent as almost entirely to occlude the lumen. Small areas of haemorrhage may be seen in some situations.

The sweat glands may be badly damaged. The secreting cells of the gland may be entirely destroyed and may have desquamated from the basement membrane, and they are often infiltrated to a considerable degree by round cells. Areas of round-cell infiltration may be found around the hair follicles, so that the hair may be embedded in the infiltrated tissue. The areas of infiltration

may coalesce to form large masses of leprous tissue. In many cases the sweat glands are destroyed except for an occasional acinus. The so-called lepra cells, so common in the chronic tubercle, are never seen in these nodules.

Lepra bacilli are most numerous just beneath the epidermis, and in this situation they are most nearly normal in form. They are to be seen in the neighborhood of the subpapillary blood vessels, in the walls of which they are often embedded; and they may be found sometimes in the lumen of a vessel. In the tissue itself the bacilli occur in clumps and many of them are in a more or less advanced stage of degeneration, which is evidenced by their inability to retain acid fuchsin. These clumps of bacilli are not evenly distributed throughout the tissue, but are isolated and occur only in masses scattered at wide intervals. Occasionally, single bacilli may be seen isolated from any others in the tissue.

The lepra bacilli are few as compared with their number in chronic lepromata, and tend to gather in the vicinity of the smaller blood vessels. We have also seen them in the cells of the hair follicles.

The reaction in the chronic tubercle is very different from that which goes on in the acute nodule. In the former the very marked sclerosis changes the normal arrangements of the layers of the epithelium in such a manner that the cells of the mucous layer, (the most elastic of the epithelial coats) are converted by the pressure exerted on them into fusiform instead of polyhedral cells (Figs. 7 and 8).

### Differential Diagnosis

In the first place the acute exacerbation of leprosy must be differentiated from other manifestations of the same disease; secondly, from certain other nodular dermatoses of different etiology, and, lastly, from other pathological entities, the symptoms of which resemble those of our syndrome.

The cutaneous tubercle of leprosy differs from the nodule which we have described above in that the latter is a typical manifestation of the chronic form of this disease and is found in conjunction with maculae, alopecias and areas of anesthesia. Moreover, the chronic tubercle appears without fever or organic reaction; it persists indefinitely and does not occur in crops. In contrast to the nodule formed in the acute exanthem, and which is a spherule, the chronic tubercle is hemispherical in form and has a flat base. The tubercle is soft and appears to have the consistence of a paste. The surface is so brilliant that it has been called "gota de aceite" (drop of oil). Among other means of differentiation between the two is the color, which in the tubercle is pale pink, modified by the color of the skin of the patient, in contrast to the deep rose color of the acute nodule. Furthermore, the sensibility of the tubercle is commonly diminished, if not completely abolished; the nodule, as we have said above, is tender. The acute nodule is painful, the tubercle never is.

Of all the other nodular skin diseases, the rheumatic erythema nodosum is the one which is most easily confused with the eruption of the acute exanthem of leprosy, especially when the acute attack is the first manifestation of this disease. The prodromal symptoms of erythema nodosum are, however, very severe in contrast to the slighter and more easily bearable onset of the acute exanthem of leprosy. The very marked erythema which has given the name to the disease, the severe pain not only on pressure but even on contact with the bed covers, the frequent localization to the arms and legs are valuable in the differential diagnosis between the two diseases. On the other hand, the variable distribution of the leprous nodules distinguishes them from the rheumatic nodules, as also does their course. If the patient has other signs of leprosy, the diagnosis is easy.

The nodules of secondary syphilis should present no difficulty in diagnosis. In the first place the history of infection and other signs of the disease such as papular and lenticular syphilides make the diagnosis between the two diseases clear, especially if the changes have persisted for several weeks. Moreover, the nodular syphilides disappear readily under appropriate treatment. The Wassermann test is of doubtful value in the diagnosis between syphilis and leprosy since a positive reaction is frequently obtained with blood from uncomplicated cases of tubercular leprosy.

If the nodules are seen in the exudative stage when desquamation is about to begin, the condition sometimes has to be differentiated from psoriasis, which however, may be distinguished by its chronic course, intense pruritus and by Auspitz' sign.

We must call attention here to the resemblance between the beginning of the acute exanthem and the beginning of other infectious diseases. When these attacks occur in known lepers, they suggest at once an exacerbation of the chronic disease. On the other hand, when they are the first signs of latent leprosy, they can be distinguished only by careful physical and laboratory examination and the observation of the patient over a period of several days.

*Prognosis.*—After an acute attack, especially a severe one, the patient may improve markedly as regards his chronic condition, a fact which is due to the quantity of bacilli and toxins destroyed and expelled from the body during the period of the acute exanthem. Although the acute attack is an indication that the microorganisms of the disease are abundant and active, it also is an evidence of a defensive reaction on the part of the host.

The prognosis is more grave when attacks follow one another in series without intermission. The outcome in such an event depends on the power of resistance (ability to form antibodies) of the patient. If the patient is able

to withstand the successive attacks, the prognosis for the improvement of the chronic condition, sometimes even almost to the point of a cure, is good. Or the improvement may manifest itself by a change from the tubercular to the nervous form of leprosy, the course of which is longer in duration and more mild.

On the other hand, if the resistance of the patient is low, he may become cachectic and die of exhaustion.

Sometimes death may be due to disease of some especial organ. When there is an organic heart or kidney lesion or when the liver is gravely affected, these organs are not able to perform their functions, and whether these old lesions are the result of leprosy or of some other cause, the acute leprotic attacks condemn the patient to death.

When large quantities of bacilli are thrown out of the body especially through the mucous membranes and the skin, ulcers may form. The organisms in these cases may be recovered from the ulcers, from the desquamated epidermis, from the saliva, from the nasal mucus and the secretions of the larynx and bronchi, from the vaginal secretion and the urine; in other words, from all the excreta of the body.

After the attack has passed, there remains the chronic stage which pursues its course with its numerous symptoms—more numerous and polymorphic than in any other disease.

*Treatment.*—A large number of remedies have been used to combat the acute exanthem of leprosy without satisfactory results: salol, quinine, arsenic, antipyretics and analgesics.

As a general rule, when chaulmoogra oil or any of its derivatives has initiated the attack, their use should be discontinued. When the attack subsides, they should be re-employed in the treatment of the chronic stage.

Our practice has been to treat the exacerbation as we would an acute infection, by daily intravenous doses of from 5 to 10 c.c. of electrargol. Collargol may be employed in the same way in doses of from 2 to 4 centigrams. These drugs lower the fever and diminish the acuteness of symptoms.

Besides this medication salicylate of soda and ichthyol may be used as a subsidiary treatment with some benefit. These drugs may be prescribed as in the following formulas:

| | |
|---|---|
| Sodii salicylatis | ʒiv |
| Ichthyolis | gr. $\overline{ss}$ |
| Syrupi simplicis | ʒii |
| Aquae q. s. ad | ʒvi |

Sig. One tablespoonful q. 2 h.

We also are accustomed to add 30 to 40 drops of the tincture of aconite to this mixture to alleviate fever and muscular pain. If the patient is very much prostrated, 6 grams of tinct. cinchonae may be substituted for the aconite, as a tonic and febrifuge. For certain patients who do not tolerate sodium salicylate we prescribe:

| | |
|---|---|
| Ichthyolis | |
| Eucalyptolis | $\overline{aa}$ gr. ii |
| Sodii bicarbonatis | q. s. ad gr. vii $\overline{ss}$ |

M. et fiat capsula No. I. Sig. One capsule q. i. d.

Locally, ointments made of ichthyol and chaulmoogra oil diminish pain.

The patient should eat nutritious and easily digested food in small amounts. Milk, eggs, legumes, etc., may be given. During convalescence tonics are indicated.

## DISCUSSION

Leprosy has been regarded as a typically chronic condition. This, however, is not the case, since, as we have shown above, the chronic course of the disease is frequently interrupted by acute attacks, a fact which makes it necessary to regard clinical leprosy in a new and different light. Leprosy is not unique in this way. Malaria, tuberculosis and syphilis, all show transitions during their course, from their ordinary chronicity to short periods of acute symptoms. These changes may be provoked by alterations in the environment; for example, in the climate, which affects the invading organism as well as the patient. Anything which destroys the equilibrium which has become established between the cells of the host and the parasite may initiate these changes, as, for example, the physiological adjustments which are evolved in the body at puberty or at the menopause. Parturition and pregnancy may cause this lighting up of the disease. Finally, just as in the case of syphilis, tuberculosis, or malaria, the institution of treatment may be followed by a recrudescence of the old and previously quiescent disease.

We have already pointed out that the institution of treatment, whether with chaulmoogra oil or its derivatives or any other medium, is frequently followed by the appearance of the acute exanthem. The dislike which patients have for the use of iodides, especially potassium iodide, is thus justified by the fact that a few days after they have taken moderate doses they are almost certain to suffer a severe exacerbation. This peculiar result may be interpreted as a reaction of the patient's body which is forced to rid itself of a huge number of injured bacilli. This acute reaction following medication is daily taken advantage of for diagnostic purposes. Large numbers of Hansen's bacilli are expelled from the body and are to be found in the mucous secretion, urine and other excretions during the acute exacerbation. The reaction of the body following treatment with iodides affords a scientific explanation for their time-worn empiric use.

We ought to speak also in this connection of the prejudice in leper hospitals against the use of fruits, specially those with an acid juice, which according to tradition are held to aggravate the disease. Pineapple and other similar fruits are instinctively excluded from the diet.

We believe that the acute exanthem of leprosy represents a defensive reaction on the part of the organism

against the invading bacilli. Facts in favor of this interpretation have been presented in various parts of this paper. They are in brief the following:

1. The excretion of large quantities of lepra bacilli from the body in the urine and through other channels.

2. The majority of excreted organisms are in a more or less degenerated condition, that is to say, the bacilli have lost to a greater or lesser extent their power of retaining acid fuchsin. Their protoplasm, either entirely or in part, shows evidence of granular degeneration, or they may be broken up into a mass of unrecognizable granular debris. In regard to this degeneration it may be said that the bacilli have undergone changes similar to those that occur in their cytoplasm after a patient has been treated for a long period with chaulmoogra oil (McDonald). It is justifiable in this connection, we think, to raise the question as to whether the granular degeneration which the bacilli undergo in the body of patients so treated is due to a direct action of the oil on the bacilli or whether it may not be the result of the action on them of some substance formed in the body of the patient under the influence of the oil. We are inclined to agree with the view of Rogers[7] that the benefit derived from this treatment is not the result of a direct bactericidal action of the oil. The fact that we found these degenerated organisms in patients suffering from the acute exanthem who have never been treated in any way would speak in favor of the latter hypothesis.

The loss of the power to retain acid fuchsin on the part of the lepra bacilli can, we think, justifiably be referred to a partial or complete destruction of the lipoid capsule of the organism upon which the acid-fast character of these bacteria is known to depend, since organisms, for example, the tubercle bacillus, which have been washed with acetone, lose their acid-fast quality in the same way*

3. The fact that these acute attacks occur in lepers who are often in remarkably good condition; and, finally,

4. The marked improvement which usually follows recovery from the acute exanthem.

These acute exanthematous attacks are, we feel, perhaps of great importance in the spread of leprosy. We believe it to be possible, in districts in which leprosy is common, that individuals may exist who have one or more mild acute attacks of leprosy, attacks which are not sufficiently severe to force them to consult a physician so that the disease is never recognized as leprosy. We have reason to believe it to be possible that such very mild attacks may occur without being followed by the chronic manifestations of the disease and that the patients may have suffered them and remained in apparently perfect health, although they have been infected by Hansen's bacillus, and may perhaps even carry the organisms for long periods of time. The fact that spontaneous cure may occur even in chronic cases of the disease is in favor of the possibility of such a hypothesis as the occurrence of very marked improvement almost to apparent cure in numbers of cases following known attacks of leprotic exanthem. It may be that the presence of carriers of this disease is responsible for the occurrence of sporadic cases of leprosy in regions in which the malady is infrequent.

## Summary

In conclusion we may state:

1. Leprosy is a chronic disease which is frequently interrupted by acute exacerbations.

2. The acute exanthem may determine the change of chronic tubercular leprosy into the maculo-anesthetic form of the disease, or vice versa.

* Since this paper was written and translated, a very important communication published by Sir Leonard Rogers in The British Medical Journal of the 7th of July, 1923, has come into our hands. Sir Leonard found, in brief, that the injection of chaulmoogra oil is followed by a return of the lipase content of the blood of lepers to the normal level below which in untreated cases of leprosy it is greatly reduced. It will require further study even to hypothecate the chain of events which are the sequelae of treatment of lepers with oil. It may be that the bacilli of Hansen are "defatted" by a lipase which is produced by the body as a counter action to the injected oil and that the benefit received by the patient may result alone from the number of organisms killed during this "defatting" process.

It is possible also that the bodies of the bacilli so devitalized and "defatted" may form an autogenous vaccine *in situ* and during their removal from the body and by an antigenic action aid in the cure of the disease. There can be no doubt that an analogous process occurs during the acute exanthem, and the sequence of events which occur during these attacks is a fascinating subject for speculation and very important investigation. Since, as we have said above, the exanthem is often induced by treatment, (Sir Leonard Rogers himself records in his article a case of this sort) it would appear possible that spontaneous attacks of this nature may, sometimes at least, be initiated by an increase of this same blood lipase, induced by physiologic processes within the body of the leper, perhaps as a result of the breaking down of the body fat or some other tissue. It is also possible to conceive of a preliminary destruction of lepra bacilli, from one cause or another, freeing sufficient of their own lipoids to increase the blood lipase, an antibody against the latter.

We have no doubt but that an increase in the blood lipase would be found to be a feature of all cases of the acute exanthem which terminate in the betterment of the patient, but what would prove to be the result in the others cannot be predicted. It must be remembered, however, that some patients derive no benefit from an acute attack, and these may correspond to the individuals recorded by Sir Leonard Rogers who are unable to respond to treatment with increased lipase production. If this be true, then in some cases the origin of the acute exanthem is independent of a preliminary production of lipase and the latter may be the result of the acute attack. A further continued investigation of blood lipase in lepers during the acute attack and in various physiological states is urgently needed.

Fig. 1.

Fig. 2.

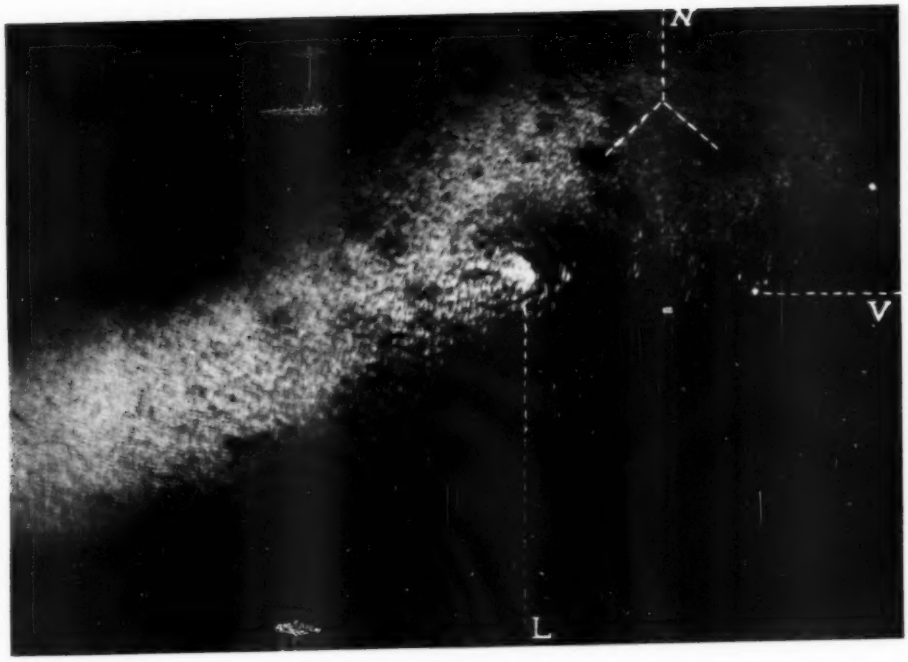



Fig. 3.

Fig. 4.

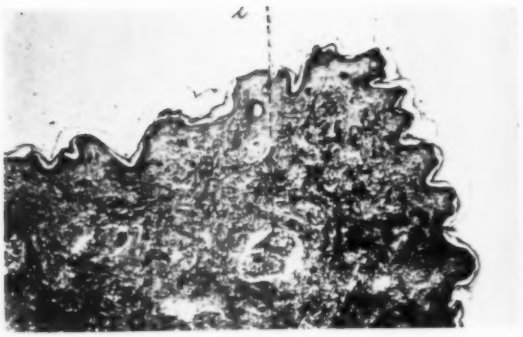


Fig. 5.

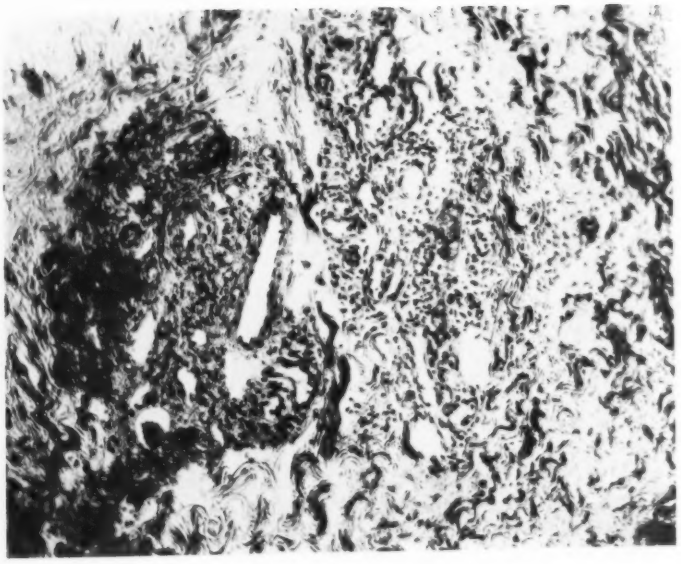


Fig. 6.

Fig. 7

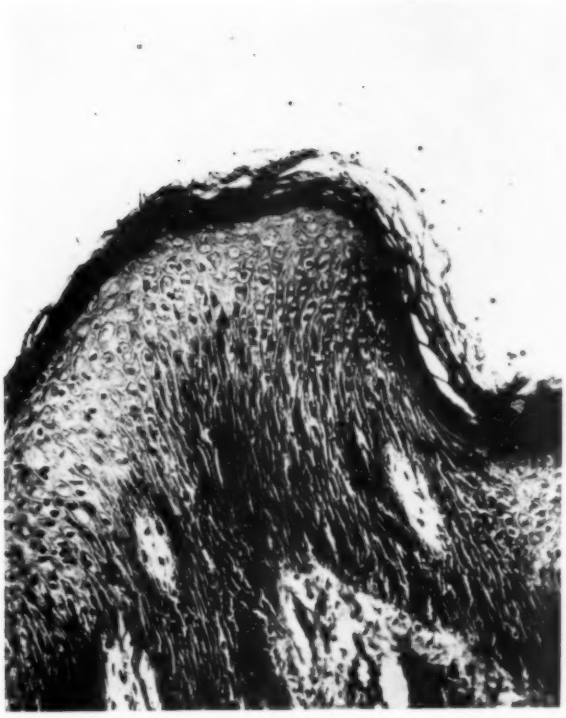


Fig. 8

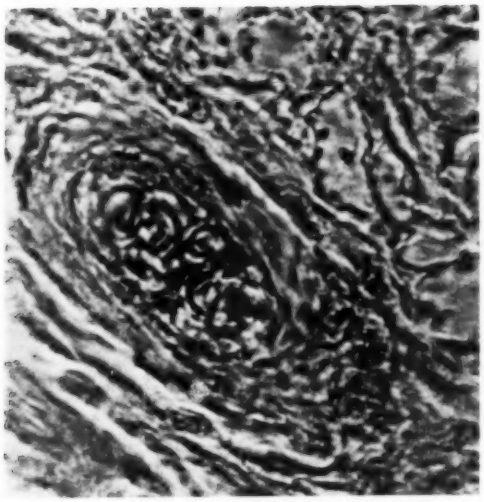


Fig. 9

3. A considerable improvement in the chronic leprosy may follow recovery from the acute exanthem. On the other hand, if the exanthem is very severe or if one attack follows another closely, a change in the type of the disease (from the maculoanaesthetic to the tubercular) or enfeeblement of the patient may considerably affect the prognosis.

4. The acute exacerbation is an indication of a defensive reaction of the host against the bacillus of Hansen and its toxins.

5. There are anatomical differences between the chronic tubercle and the acute inflammatory nodule.

6. The patients who have sufficient resistance to overcome successfully the acute exanthem of the disease are those who obtain the most favorable results from the treatment.

7. During the course of the exanthem the bacillus of Hansen undergoes certain degenerative changes preparatory to its excretion from the body in the urine or elsewhere.

8. During the acute exanthem of leprosy the patients excrete a larger number of organisms than during any other stage of the disease.

## DESCRIPTION OF CHARTS

Chart I.—Ch. S., native of Somondoco, aged 23, hospital of San Raphael. This attack went on to ulceration. Shows the temperature curve from a case of acute exanthem of leprosy. The fever terminates by a typical lysis. At A and B are seen the falls in the temperature which followed, respectively, the administration of electrargol and sodium salicylate.

Chart II.—E. C., native of Ubaté, aged 23 years, hospital of San Raphael. Showing the termination by lysis of the fever in an acute exanthem.

Chart III.—B. M., 18 years, native of Guenza, hospital of San Raphael. Shows the temperature curve of a girl in whom the subsidence of one acute exacerbation of chronic leprosy was followed in a few days by the onset of a second attack. The slow lysis which terminated the fever of the first attack is followed by a gradual rise in temperature which represents the prodromal fever of the second exanthem. It is interesting to note the descent of the temperature curve during the menstrual period.

Chart IV.—S. G., aged 13 years, native of Chocontá, hospital of San Raphael. First acute exanthem. Shows a very irregular curve of temperature in a patient who had successive acute exanthems, three in number. The administration of collargol was followed, as in the Chart I, by a fall of temperature. The third attack followed immediately on the second without any descent of the temperature maintained during the second attack. After the third attack the fever ended by lysis.

## DESCRIPTION OF FIGURES

Fig. 1.—Shows a patient in the early eruptive stage of the acute exanthem. At this time the cutaneous nodules are appreciable only on palpation. The skin of the face and arms, however, is covered with a blotchy bright rose color eruption. This patient was a mestizo.

Fig. 2.—This patient, a mestizo boy, shows a stage of the eruption of the acute exanthem later than that shown in Fig. 1, beneath the skin of the face especially over the malar region and in the region of the naso-labial groove. The nodules, which are the primordial elements of the eruption, have grown sufficiently to be visible.

Fig. 3.—This figure was a photograph of the posterior aspect of the elbow of a young girl with the acute exanthem of leprosy. It shows large numbers of discrete nodules over which the skin was discolored (N). At (L) several of these nodules have coalesced to form a leproma. At (V) a nodule may be seen, at the center of which a vesicle has formed and which is on its way to terminate by ulceration (see page 150).

Fig. 4.—Terminal stage of the acute exanthem which has run its course without ulceration. As the picture shows, the skin is much roughened and desquamation is about to begin. The skin of a patient in this condition has a purplish color which gradually changes to a bronzed hue. This patient was a young girl employed as a cook who was admitted to a local hospital with a diagnosis of typhoid fever. This fever, after examination, was seen to be the acute exanthem of leprosy, which in her case was the first clinical manifestation of that disease.

Fig. 5.—Section through a cutaneous nodule removed during the course of an acute attack of leprosy. It shows the multiple areas (i) of infiltration with mononuclear cells lying about distended vessels in a matrix of dense connective tissue.

Fig. 6.—An area of mononuclear infiltration about the distended vessels in a nodule of acute leprosy. The figure also shows the dense hypertrophied bundles of white fibres around the area, which contrast sharply with the delicate connective-tissue stroma of the infiltrated area.

Fig. 7.—Microphotograph of the cutaneous epithelium over an acute nodule taken from a case of acute exanthem of leprosy. The cells of the mucous layer of Malpighi have retained their normal polyhedral form.

Fig. 8.—This picture, which is of the same magnification as the preceding one, shows the epidermis of a chronic tubercle taken from the patient from whom the skin pictured above was removed. The cells of the mucous layer of Malpighi have assumed a fusiform aspect as the result of contraction of adjacent tissues following fibrosis.

Fig. 9.—Photograph of a blood vessel in the cutis vera highly magnified (× 1500) to show a small mass of granular lepra bacilli in the lumen of the vessel. The bacilli have been retouched.

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# EXPERIMENTS ON THE EXTRAHEPATIC FORMATION OF BILIRUBIN

By Ella Hutzler Oppenheimer

*(From the Department of Pathology, The Johns Hopkins University)*

Some years ago, Whipple and Hooper [1] carried out a series of experiments from which they concluded that hemoglobin introduced into the circulation from which the liver was excluded can be transformed into bilirubin within two hours. Recently McNee and Prusik [2] have reported their failure to confirm these conclusions; and Rich [3] has demonstrated that the liver is not actually excluded from the circulation by the methods used by Whipple and Hooper. Rich found that, if the liver is extirpated and the conditions of their experiments then reproduced, none of the hemoglobin will be transformed into bilirubin in a period as long as five and a half hours after the removal of the liver, even though a much more delicate test for the pigment was used. His conclusion was that under normal conditions the liver is necessary for the transformation. Mann and Magath,[4] on the other hand, after reducing the hepatic circulation for a number of weeks before removing the liver, found that bilirubin can be detected in the plasma in a few hours after hepatectomy. However, certain considerations which will not be entered into here leave the matter of the normal site of origin of bilirubin still open for investigation.

Actual experimental observations dealing with intravascular extrahepatic bilirubin formation are not numerous and it is of importance to re-examine experimentally the few isolated and contradictory experiments which are now on record. The present report, therefore, deals with an examination of a certain experiment which has been put forward as a conclusive proof that hemoglobin can be transformed into bilirubin locally within the blood vessels outside the liver.

Jones and Jones,[5] working on a patient with paroxysmal hemoglobinuria, have reported that they isolated an arm from the general circulation—and thereby from the liver—with a sphygmomanometer arm band by means of which the pressure on the arm was maintained at a level higher than that of the systolic blood pressure, which in this patient was 118 millimeters of mercury. They then induced a local hemolysis in the vessels of the isolated arm by immersing it in ice water. Twenty minutes after the hemolysis had begun, the serum from the arm was reddish yellow and showed great quantities of hemoglobin but no bilirubin. *Thirteen minutes later*, that is, thirty-three minutes after the induction of hemolysis, the serum was dark yellow, showed a much smaller amount of hemoglobin and gave a positive test for bilirubin by the Gmelin method. Serum from the general circulation taken before the arm band was removed gave a negative Gmelin test and showed no hemoglobin. From this they concluded that hemoglobin can be changed into bilirubin in the larger vessels, capillaries and tissue spaces of an isolated extremity, without the intervention of the liver.

In view of the experiments mentioned in our first paragraph, it was important to examine experimentally the statement that hemoglobin can be transformed into such large amounts of bilirubin * in stagnant blood outside the liver in so short a time. It was decided, therefore, to isolate an extremity of an animal completely from the circulation, and then to observe whether bilirubin would be formed from free hemoglobin within the blood vessels of the isolated member.

## Experimental

The dog was used as the experimental animal. The Van den Bergh [6] reaction which permits detection of bilirubin in quantities as small as 1 in 1,500,000 was the test used. Only three experiments were performed, as the results were so perfectly clean cut.

All operative procedures were carried out under morphine and ether anaesthesia. A cannula was first inserted into the external jugular vein and about 50 c.c. of blood was allowed to run into sodium citrate. This was

* The Gmelin test can reveal the presence of bilirubin only in concentrations above 1 to 40,000 in albuminous fluids; an actual tissue jaundice appears when the concentration reaches 1 to 60,000.

centrifugalized and the supernatant plasma tested for bilirubin as a control to determine that there was no bilirubinaemia to start with. A second control test was carried out, human blood serum being used (bilirubin occurs here in a concentration of about 1 to 1,000,000 up to 1 to 400,000), in order to demonstrate the efficacy of the reagents used. After the supernatant plasma had been pipetted off, the packed red cells were twice washed in 0.9% sodium chloride solution and centrifugalized. Following the second centrifugalization, the packed red cells were laked in 25 c.c. of distilled water. While the cells were being washed for laking, the animal was prepared for the experiment. A midline incision was made and the aorta and inferior vena cava were dissected clean just above their bifurcations. A ligature was placed under each so that they could be quickly tied. Then an incision was made through the skin and subcutaneous tissue around the upper third of the thigh of each leg in order to stop any collateral circulation through the cutaneous vessels. The laked red cells were then slowly injected into the jugular vein.

In the first experiment, two minutes were allowed to elapse after the injection in order to enable the hemoglobin to circulate thoroughly. Then the vena cava was tied securely and immediately afterwards the aorta was tied and cut between two ligatures. In the second and third experiments, we waited four minutes after the injection before tying the vessels. By tying the vena cava first, we hoped to dam back enough blood into the extremities to give us a plentiful supply during the experiment and also to reproduce the condition which occurs when a tourniquet is applied.

In the first dog, in order to demonstrate that there had been no collateral circulation, the limbs were entirely severed from the body before the dog was killed. There was no active or continued bleeding from any of the vessels. In the second and third dogs, an added precaution was taken to guard against any collateral circulation. After tying the vena cava and aorta above their bifurcations, the muscles of the upper third of the thighs were cut through to the bone, the sciatic nerves alone being left intact. After the completion of the experiments, the femur was in every case broken in two. There was no oozing of blood from the broken surfaces. Therefore, in all three cases, it was demonstrated satisfactorily that the blood in the isolated extremities had absolutely no connection with the general circulation.

The first dog was killed three hours and twenty minutes after the injection of the laked blood; the second died four hours and five minutes after the injection, and the third lived six hours and fifteen minutes after the hemoglobin was introduced into the blood stream. Small samples of blood were taken at varying intervals from the cannulated jugular and femoral veins. At first, it was attempted to obtain the blood from the femoral vein with a syringe but this was found to be unsatisfactory because of the lack of circulation in the isolated extremities. However, blood was obtained readily from the cannula by raising the leg and gently milking it.

In every case the color of the serum remained claret red to the end of the experiment. In no instance was even a trace of bilirubin demonstrable by the Van den Bergh test, which was cleanly negative in each experiment. The control tests on human serum containing small amounts of bilirubin were always sharply positive.

EXP. I.

| Sample | Time | Time after injecting HB. | Circulation | Color of serum | Van den Bergh |
|---|---|---|---|---|---|
| 1 | 10.50 | Control—before | General | Faint pink* | Negative |
| 2 | 1.00 | 10 min. | Right leg | Claret | Negative |
| 3 | 1.35 | 45 min. | Right leg | Claret | Negative |
| 4 | 2.25 | 1 hr. 35 min. | Left leg | Claret | Negative |
| 5 | 3.25 | 2 hrs. 35 min. | Right leg | Claret | Negative |
| 6 | 3.50 | 3 hrs. | Left leg | Claret | Negative |
| 7 | 4.30 | Control serum | Human | Straw | Positive |

* Slight amount of hemolysis.

EXP. II.

| Sample | Time | Time after injecting HB. | Circulation | Color of serum | Van den Bergh |
|---|---|---|---|---|---|
| 1 | 11.30 | Control—before | General | Colorless | Negative |
| 2 | 1.30 | 1 hr. | Right leg | Claret | Negative |
| 3 | 2.30 | 2 hrs. | Left leg | Claret | Negative |
| 4 | 3.30 | 3 hrs. | Right leg | Claret | Negative |
| 5 | 4.30 | 4 hrs. | Left leg | Claret | Negative |
| 6 | 4.45 | Control serum | Human | Straw | Positive |

EXP. III.

| Sample | Time | Time after injecting HB. | Circulation | Color of serum | Van den Bergh |
|---|---|---|---|---|---|
| 1 | 11.15 | Control—before | General | Colorless | Negative |
| 2 | 1.05 | 30 min. | Right leg | Claret | Negative |
| 3 | 2.05 | 1 hr. 30 min. | Right leg | Claret | Negative |
| 4 | 3.35 | 3 hrs. | Right leg | Claret | Negative |
| 5 | 5.35 | 5 hrs. | Right leg | Claret | Negative |
| 6 | 6.50 | 6 hrs. 15 min. | Right leg | Claret | Negative |
| 7 | 7.00 | Control serum | Human | Straw | Positive |

## SUMMARY

From the description of the above experiments, it can be seen that, when hemoglobin is suddenly liberated into the plasma of a normal dog and the extremities are immediately isolated from the general circulation, none of the hemoglobin is transformed into bilirubin within an isolated extremity during a period as long as six and a quarter hours. Jones and Jones, however, report that the transformation of hemoglobin into bilirubin will take place within thirty-three minutes in the isolated arm of a

patient with paroxysmal hemoglobinuria. Our experiments make us feel that this transformation would not occur within the vessels of a normal individual if the extremity were completely isolated from the general circulation. Otherwise we must assume that the blood vessels of the paroxysmal hemoglobinuric differ in function from those of normal individuals or else there must be a fundamental difference between the bilirubin forming potentialities of the vascular endothelium of the dog and man. Since the conclusions of Jones and Jones are drawn from only a single observation, it is important that further similar studies be carried out on patients of this type.

Jones and Jones are careful to draw the conclusion that *under abnormal conditions* hemoglobin can be transformed into bilirubin without the intervention of the liver, although they suggest that a large part of the transformation of hemoglobin into bilirubin could occur normally within the blood vessels outside the liver. Up to the present, there exists not a single experiment or observation which demonstrates the formation of bilirubin within the circulation outside the liver in the normal animal or man. Observations on patients have been confined to cases with longstanding disturbances of hemoglobin metabolism; in animals, the positive results of Mann and Magath were obtained in dogs in which the blood supply to the liver had been greatly reduced over a period of weeks before the experiment was carried out. In view of these facts, further experimental evidence must be accumulated before we can regard the question of the normal site of origin of bilirubin as settled.

I wish to express my appreciation to Dr. Arnold R. Rich for suggesting that I investigate this subject.

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# NOTES ON NEW BOOKS

*The Colloidal State in its Medical and Physiological Aspects.* By Sir William Bayliss. *(Oxford Medical Publications, London. Henry Frowde; Hodder & Stoughton, 1923.)*

The purpose of this short monograph of some ninety odd pages "is to be regarded as an attempt to give a short account of the properties of colloids, so far as of interest in connection with the phenomena occurring in living beings." The book is evidently intended to give a brief description of colloidal phenomena to those who are more or less unfamiliar with the subject, and it serves this purpose well. The nature of the colloidal state, the importance of the large surface of colloids giving rise to adsorption phenomena, their osmotic pressure and its relation to certain physiological processes, and the physiological action of colloids, are among the subjects discussed. A final chapter on proteins and hemoglobin emphasizes the adsorption point of view more than the chemical one recently so ably advocated by Loeb. E. K. M.

*Diseases of the Stomach and Upper Alimentary Tract.* By Anthony Bassler, M. D., F. A. C. P. $8.00. *(Philadelphia, F. A. Davis Company, 1922.)*

Every physician will endorse that part of the author's preface which stresses the necessity of a knowledge of "practical chemistry, physiology, physiological chemistry, morbid histology, bacteriology, etc." as well as his advice regarding the importance of engaging for some years in "observation and experience in general medicine" before entering the special field of gastro-enterology. Very properly, too, he directs attention to the dyspeptic who is often afflicted, primarily, with circulatory, respiratory, renal and other disorders producing secondary manifestations of digestive disturbances, and who may be more intelligently and successfully treated by those specializing in these respective branches.

The topographical and histological anatomy of the digestive tract are well described and the illustrations are pertinent. Physiology and chemistry are thoroughly discussed, but nothing new is presented; and the same may be said of the chapters covering anamnesis, history records and examination of patients. Much space is devoted to "Roentgen Rays in the Diagnosis of Stomach Diseases," and the illustrations and descriptive tests are good.

The various laboratory tests employed in the estimation of motor, secretory and other powers of the digestive tract are dealt with at length.

The author lays great stress upon the importance and value of the Rehfus Fractional method of gastric analysis, despite the fact that later studies and observations in many of the larger clinics by competent diagnosticians have brought this method into disfavor, the consensus of opinion being that secretory capacities are relative only, and that the single extraction in the vast majority of cases will give results equally as valuable as those secured by this tedious and prolonged method with its many and variable curves.

In the chapter on "Microscopic Examination of Gastric Contents" the statements regarding the great diagnostic importance of finding shreds of mucous membrane or tumor particles are open to criticism. Certainly, it is not a common occurrence to discover, in wash-water, particles of membrane, the study of which will give valuable information!

The "Significance and Methods of Examination of Feces in Gastric Disease" are well presented, but the illustrations are poor.

The chapters dealing with diet, therapeutics and indications for surgery are full and interesting; they show that the author is thoroughly conversant with the most recent and best work along these lines. Consideration is given to various

diseases of the digestive tract, and the author is to be commended for his comprehensive and illuminating presentation, which is greatly to be desired in a textbook of this character.

All in all, this book may be heartily recommended to physicians and students interested in this important branch of medicine. E. H. G.

*A Textbook of the Practice of Medicine.* By Various Authors. Edited by Frederick W. Price. *(London. Henry Frowde; Hodder & Stoughton, 1922.)*

Nothing is more urgently needed in internal medicine at the present time than a good one volume textbook. The older classics, despite their excellent descriptions of disease pictures, now represent an antiquated viewpoint and to be of real use to the modern physician something must be written which approaches the subject from an entirely new angle.

Unfortunately, one's hopes are immediately dashed on opening the volume which we herewith review. One finds merely the old schematic method of treatment, definition, etiology, pathology, etc., and even that, it seems to us, is done here in a particularly unfortunate way. One might mention a few of the outstanding delinquencies: the discussion of diabetes, one of the most important diseases with which we have to deal, is covered in a few pages, the remarks on treatment being a perfunctory summary of the views of Allen and Joslin, quite inadequate actually to guide the practitioner in the care of a particular case. Under scarlet fever we read—in spite of the recent bacteriological work to the contrary—that the causal agent is entirely unknown. The discussion of nephritis again brings out no new point of view, but is merely a monotonous repetition of the old line classification, parenchymatous, interstitial, and other types. The section on disease of the heart is so split up and built on a scheme of more or less illogical classifications that the reader is left in a state of confusion as to whether or not mitral insufficiency and auricular fibrillation are different diseases or whether they may have any point of contact.

In short, we can say nothing in favor of this book in so far as it adds anything to what is already easily accessible to the physician. It is to be hoped that in the near future some inspired author will cast aside the old fashioned textbook and write a treatise on medicine which is a worthy presentation of thought and opinion. A. L. B.

*Exercise in Education and Medicine.* By R. TAIT MCKENZIE, M. D. Cloth, $5.00. *(Philadelphia and London, W. B. Saunders Company, 1923.)*

The third edition of this interesting book comes to us at a most opportune time. The problem of exercise for medical students has long been a pressing one.

Moreover, as preventive medicine gains in importance and as the hygienic care of patients requires more and more definite instructions, scientific knowledge about exercise becomes increasingly needed by the physician.

Dr. McKenzie's studies along these lines and his contributions in corrective gymnastics are distinctive. Outside of Philadelphia he is best known as a sculptor of athletic figures.

This book gives one a comprehensive idea of the various schools and theories of exercise. It could be studied with benefit by all medical students, especially if a practical course in physical culture were a required part of their curriculum. It could there be made to serve the double end of maintaining the health of the medical student, while instructing him in that most useful of all therapeutic methods—properly directed exercise. H. M. T., Jr.

*The Examination of Patients.* By NELLIS B. FOSTER, M. D. Cloth $3.50. *(Philadelphia and London, W. B. Saunders Co., 1923.)*

The examination of patients is more nearly a scientific procedure today than ever before. Gone are the times of biliousness and a "touch of malarial fever," and the clinician is now called upon by a medically educated laity to produce a complete and definite diagnosis. The great advances in diagnosis have been made very largely by studying patients simultaneously with modern methods of precision (specialized chemical methods or instruments such as the electrocardiogram) and with the old bedside procedures. From this combination there has evolved a type of enlightened practice the results of which far exceed those of former days. During this evolution the discoveries and progress occurred largely in the laboratory, and, in fact, will continue to do so. Many steps necessary to laboratory progress are valueless to the patient and at the present day many facts at first discovered and discoverable only in the laboratory can be observed by the physician trained in both ways.

From time to time it is necessary to draw breath and sum up the situation, to clean the slate of useless side figuring and allow the facts of importance to be clearly seen and understood. This is Dr. Foster's intention—to give to the physician and medical student the best useful methods of examining patients by the trained senses combined with laboratory procedures.

As the author says in the preface, "Refinement of diagnosis compels the use of trained senses of touch, sight, and hearing. The development of laboratory methods has diverted attention from these fundamentals."

One great advantage this book has over others written on clinical diagnosis is that all non-essentials have been omitted. A good consultant uses constantly all the methods and procedures here described.

Here the physician finds described the methods needed to put him in touch with the various specialists; here the student finds in concise form the assembling of his various studies into a coordinated whole.

No attempt has been made by the author to include clinical microscopy in this book, and this seems to me a wise move. To have broadened the subject in this way would have served to obscure the real purpose.

Dr. Foster, on account of his great experience as a clinician who has never lost his intimate touch with the laboratory, is peculiarly fitted to write such a work. He has outlined the methods which he has found reliable in his practice as an internist. It is quite possible that specialists may consider the chapters devoted to their field somewhat brief and lacking in completeness, but it must always be remembered that each subject is approached from the general physician's point of view and not from that of a specialist.

The illustrations have been well selected and round out a work which may boast a most refreshing brevity.

H. M. T., Jr.

*Food for the Diabetic.* By MARY PASCOE HUDDELSON, with an introduction by NELLIS BARNES FOSTER, M. D. Cloth, $1.25 *(New York, The MacMillan Company, 1923.)*

"The purpose of this book is to give diabetic patients, briefly and in simple language, the information of the nature of their disease from a dietetic standpoint that is necessary in order to carry out their physician's directions." The great obstacle to the proper management of diabetic patients in their

homes is the difficulty of instructing them in the calculation and preparation of menus for food weighed in accordance with a physician's prescription for so many grams of protein, fat and carbohydrate. Very convenient food tables are provided here with equivalent weights in grams and ounces and instructions to the patient as to the measurement of the foods with simple household utensils such as: a standard tablespoon, a knife, a standard teaspoon, a ruler, and a half-pint glass measuring cup. A Chatillon gram scale with a movable disk is recommended. The presentation is clear and simple. Any literate patient of average intelligence should be able to learn to prepare weighed diets in a short time by following this little manual. Many excellent recipes are given. It is a book which promises to be of great usefulness to all those who face the difficult task of teaching the diabetic how to live outside a hospital. W. S. M.

*The Clinical Method in the Study of Diseases, with a Biographical Note on the Life of Dr. Horace Dobell.* By R. M. Wilson. Cloth, $1.50. *(London, Oxford Medical Publications, 1921.)*

This little volume is a plea for a return to the methods of clinical study of which Dobell was the exponent. With what the author has to say about the necessity for preserving and cultivating the art of clinical observation everyone must agree. A protest is made against the domination of the clinic by the laboratory. One feels that the author would not be content merely to make the laboratory subservient to the clinic, but that he would gladly eliminate the laboratory entirely. In this respect his zeal carries him to the point of making such an absurd statement as this: "The discovery of a bacillus never yet solved a fundamental problem of disease."

W. S. M.

*Materia Medica for Dentists.* By Frank Coleman. Fifth edition. *(London. Henry Frowde; Hodder & Stoughton, 1922.)*

As the author states in the preface, this work is "not a complete treatise on Dental Materia," but rather a brief enumeration of the generally accepted opinions relating to the pharmacology and dental therapeutics of the main agents of importance to the dental practitioner.

The grouping according to pharmacologic classification, although faulty, is the most practical, and decidedly more scientific than that according to alphabetic sequence, notwithstanding the overlapping which is inevitable.

The description of each drug is good, although too brief, and lacks the notation of agents, synergistic and antagonistic.

The chapter on prescription writing is too incomplete for a student properly to understand and apply, and must be augmented considerably in the classroom.

To summarize, the arrangement and the order of treatment of agents, with the clear manner of stating facts pertaining thereto, are all that can be desired, and as a handy reference book for the most important information concerning drugs of dental import, the book serves the purpose for which it is intended. E. H. & H. H. S.

*The Tonsils.* By H. A. Barnes, M. D. Second edition, $5.00. *(St. Louis, C. V. Mosby Co., 1923.)*

This book on the tonsils by Barnes supplies a very definite need among laryngologists and students, as it contains one of the few descriptions, available in English, of the histology of the tonsils. This description is supplemented by many microphotographs. The revised edition, however, adds very little that is new to this section. A clear conception of the anatomical arrangement of the blood vessels in the tonsil and the structure of the crypt as the morphological unit is very necessary to an understanding of the modes of infection and yet these are noticeably lacking from the description.

The pathology is less complete than the histology, especially as regard the changes produced by chronic inflammatory reactions, which constitute the major part of tonsillar pathology. The attempt to correlate the pathological with the clinical changes is very commendable.

The new material in this edition consists principally of new types of operations. Possibly an elucidation of the general principles of the operation with a comparison of results of the different procedures would eliminate many of the so-called new operations. The indications for operation are presented in a very helpful manner.

The sections on focal infection and the roentgen ray treatment of chronic tonsillitis are good résumés of the current views on these subjects. Also, they are not too enthusiastic, and may be used as a general working guide. P. McC.

*Environment and Resistance in Tuberculosis. Rest and Other Things.* By Allen K. Krause. Cloth, $1.50 each. *(Baltimore, Williams and Wilkins Co., 1923.)*

Among the contributions of the past year which are of great interest and usefulness to the general physician are the two volumes by Krause entitled "Rest and Other Things" and "Environment and Resistance." In tuberculosis above all diseases the general reader has been beset, on the one hand, by rigid and abstruse laboratory reports and, on the other, by loose and perhaps often unsound clinical expositions. The great contribution of Krause's writings in the past few years, as illustrated, for example, by the essays on tuberculosis which have appeared from time to time in the Journal of the Outdoor Life, has been the correlation, by a scientifically trained worker, of the facts from the laboratory with the natural history of the disease as it actually appears in man. The volumes referred to are for the most part elaborations of previous essays and addresses. We wish especially to call attention to the article on resistance. The writer's idea throughout is to avoid as far as possible the vague designations "virulence of organism" and "resistance of host" which actually mean very little, and to analyze in a concrete way those factors which really do seem to lead to greater "resistance" or to "susceptibility" in tuberculosis. Krause stresses first the accidental factors in resistance—the accidents of dosage, the accidents of time, the accidents of place, and the accidents of stress. For example, few of us stop to realize that the caseation and rupture of a lymph node, into the thoracic duct, on the one hand, and, on the other, into the mediastinal tissues means all the difference between an acute miliary tuberculosis and a latent and unnoticed event. In other words, many a patient clearly develops manifest, perhaps fatal, tuberculosis through chance occurrences without the need of postulating any fundamental and general lowering of resistance. Krause next discusses the mechanism of the healing or progress of the tuberculous lesions, stressing the importance of balance between the two processes of caseation and fibrosis which make respectively for advance or retardation, and again emphasizing the varying elements which may promote one or the other of these processes. Finally, there is an admirable discussion of the allergic element in relation to "resistance" and "susceptibility" in tuberculosis. Needless to say, the ultimate chemical and physical problems are left unsolved, but a reasonable and satisfactory background is furnished in which to "set" the phenomena of the disease as they occur clinically. A. L. B.

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